



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> :  A61B		A2	(11) International Publication Number: <b>WO 92/20273</b>  (43) International Publication Date: 26 November 1992 (26.11.92)
<p>(21) International Application Number: PCT/US92/04153            (22) International Filing Date: 18 May 1992 (18.05.92)</p> <p>(30) Priority data:            701,127 16 May 1991 (16.05.91) US</p> <p>(60) Parent Application or Grant            (63) Related by Continuation            US 701,127 (CIP)            Filed on 16 May 1991 (16.05.91)</p> <p>(71) Applicant (for all designated States except US): NIM INCORPORATED [US/US]; 3624 Market Street, Suite 508, Philadelphia, PA 19104 (US).</p>		<p>(72) Inventor; and            (75) Inventor/Applicant (for US only) : CHANCE, Britton [US/US]; 4014 Pine Street, Philadelphia, PA 19104 (US).</p> <p>(74) Agent: WILLIAMS, John, W.; Fish &amp; Richardson, 225 Franklin Street, Boston, MA 02110-2804 (US).</p> <p>(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.</p> <p><b>Published</b>  <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p><b>(54) Title:</b> HEMOGLOBINOMETERS AND THE LIKE FOR MEASURING THE METABOLIC CONDITION OF A SUBJECT</p> <p><b>(57) Abstract</b></p> <p>An oximeter for determining the oxygenation state of localized body tissue per se, constructed to be worn over a period of activity by a user and comprising a flexible, body-conformable support member which supports, adjacent the skin of a user, over the localized tissue of interest, at least a pair of spaced apart light sources, and intermediate thereof, at least a pair of wavelength-specific photo detectors, each light source exposed to transmit wavelengths of both of said specific wavelengths toward the localized tissue of interest lying below the skin and below the associated subcutaneous fat layer of the user, and each detector exposed to receive photons of the respective specific wavelength that have originated from each light source, and scattered from the localized tissue and passed back to the detectors through the subcutaneous fat layer and skin of the user, the support member including conformable barrier means disposed between each light source and the detectors, said barrier means being of substance capable of conforming to the contour of the wearer and preventing light energy proceeding laterally in the region of the barrier means from reaching the detectors.</p>			

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HEMOGLOBINOMETERS AND THE LIKE FOR MEASURING  
THE METABOLIC CONDITION OF A SUBJECT

Background of the Invention

5 In one aspect, the present invention relates to wearable apparatus for noninvasive determinations of the concentration of oxygen in a specific target region of tissue. More specifically, the present invention discloses a user-wearable system for monitoring the  
10 oxygen concentration, or oxygenation trend, in the tissue of a subject undergoing aerobic stress, such as an exercising person.

The increasing popularity of all forms of exercise over the last several decades has also lead to an  
15 increased interest in the measurement of individual athletic performance. However, at the present time, athletes are limited to obtaining heartbeat and blood pressure data while they are exercising. Although of some use, these data do not reflect peripheral  
20 circulatory capacity or the oxygenation state of specific muscle tissue.

In order to measure oxygen delivery to the capillary bed of the muscles, an athlete must be tethered to electrocardiogram apparatus and have blood samples  
25 drawn while running on a treadmill. These are essentially operating room apparatus and procedures, which do not simulate the actual conditions of exercise. The measurement of aerobic efficiency by analyzing the oxygenation state of a particular muscle while exercising  
30 is important due to a variety of reasons. For example, as a casual jogger strives to become a marathon runner, the efficiency at which he/she uses oxygen can severely impact performance; data reflecting the utilization of oxygen can provide information which allows an athlete to

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change pacing strategies or otherwise adjust their activity to produce better results. Other athletes, such as swimmers, cyclists and rowers would also find this information useful for evaluating performance. However, 5 the use of blood oxygenation data is not limited to competitive athletes; even geriatrics who undergo mild aerobic exercise to maintain and improve their health can benefit from data concerning the changes in blood oxygenation brought about by exercise or other activity. 10 Other animals, such as racehorses, can also benefit from this type of performance data. By measuring the oxygen delivery to the muscles, both the quality of training and the natural ability to exercise may be evaluated.

In addition to monitoring and maximizing athletic 15 performance, information pertaining to the delivery of oxygen to the limbs and the brain is important in military and space applications where changes in gravity and other stresses may result in fatigue, and ultimately, blackouts.

20 Although apparatuses which measure the oxygenation content of blood using data collected from a fingertip or ear lobe are available, these devices do not actually measure the oxygenation state of nearby muscle groups or the brain. To monitor athletic performance, or the 25 condition of exerted muscles, data collection must be performed at the site of interest. For example, runners will wish to be provided with this information during a race, not in a laboratory. Therefore, for an apparatus measuring the metabolic condition of an athlete to be 30 truly useful, a rugged, lightweight, user-wearable system must be provided.

One method by which the oxygen level in a muscle may be measured is tissue spectrometry. For example, red and near-red light, having wavelengths between about 600- 35 800 nanometers (nm), will harmlessly penetrate body

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tissues. As the light penetrates the tissue, it migrates and is absorbed by deoxygenated hemoglobin in small blood vessels. Normally, tissue receives oxygen from hemoglobin contained in red blood cells, which circulate 5 in the major blood vessels and eventually into the capillary bed, supplying muscle tissue with oxygen. Aerobic activity can cause the level of oxygen use to rise, causing a commensurate rise in the level of deoxyhemoglobin which is compensated for by increased 10 blood flow in trained individuals. Near-red light is absorbed by tissue that is not receiving as much oxygen as the surrounding tissue due to increased levels of deoxyhemoglobin in less trained individuals. Thus, by determining the amount of incident radiation absorbed, 15 the oxygenation state of a specific area of tissue, and the training level of an individual, can be determined.

The present invention also relates to a study of the linkage between cerebral activity and oxygen delivery and oxidative metabolism in the brain tissue. During a 20 brain activity, blood flow can be studied using PET or NMR. Faster electrical and magnetic responses can be measured using EEG and MEG. While these techniques eventually might be able to provide examination and screening for neuronal deterioration and/or deterioration 25 of brain function, they are relatively expensive and not suitable for emergency treatment situations wherein the diagnostic equipment should be taken to a patient. Optical techniques, on the other hand, might provide a suitable, cost effective alternative for examination and 30 screening of a tissue of an organ.

#### SUMMARY OF THE INVENTION

The present invention provides a novel, wearable system for determining the metabolic condition of an aerobically stressed portion of the muscle tissue of an 35 exercising person. The system comprises a lightweight

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rugged detector, worn against the skin surface of the subject, adjacent to the muscle being monitored. The system of the present invention thus minimizes any performance impairment. The preferred system further 5 comprises a wearable power pack and a wearable display means for displaying information indicative of the aerobic metabolic condition of the region being monitored. In a preferred embodiment intended for use while running or engaged in similar athletic activities, 10 the display is worn on the wrist and displays information from a leg-mounted detector. In another embodiment, intended to provide information to coaches, a telemetry system is employed to transmit a signal carrying the data from the detector to a remote location, for processing 15 and display.

The detector of the present invention preferably employs a continuous wave spectrophotometer having one or more sources of electromagnetic radiation with wavelengths between about 760 nanometers and about 800 20 nanometers directed into the tissue of the subject. The detector is efficiently coupled to the body tissue and utilizes the principle of photon migration to detect the portion of the transmitted radiation arriving at an adjacent skin region.

25 The present invention also discloses methods for displaying the aerobic metabolic condition of a subject. The percentage of deoxyhemoglobin in the blood of the subject is determined, and a signal representative of this percentage is converted into a graphic 30 representation. The display may preferably be a digital display, a bar graph or a series of deoxyhemoglobin levels, placed on a time scale.

OBJECTS AND FEATURES OF THE INVENTION

It is an object of the present invention to 35 provide methods and apparatus which allow a rapid

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determination of the oxygenation state of tissue, such as muscle tissue, located beneath the surface of the skin of a subject, such as an athlete, without requiring the subject to be tethered or physically connected to 5 laboratory or operating room monitoring equipment.

It is also an object of the present invention to provide apparatus which may be attached to a user which would determine the oxygenation state of a portion of the user's body and provide that information in a readily 10 understandable form.

It is a further object of certain embodiments of the present invention to provide information pertaining to the oxygenation state of tissue directly to a user wearing the apparatus of the present invention.

15 It is another object of certain embodiments of the present invention to transmit information pertaining to the oxygenation state of tissue to a remote observer.

According to one aspect of the invention, an oximeter is provided for determining the oxygenation 20 state of localized body tissue per se, constructed to be worn over a period of activity by a user and comprising a flexible, body-conformable support member which supports, adjacent the skin of a user, over the localized tissue of interest, at least a pair of spaced apart light sources, 25 and intermediate thereof, at least a pair of wavelength-specific photo detectors, each light source exposed to transmit wavelengths of both of the specific wavelengths toward the localized tissue of interest lying below the skin and below the associated subcutaneous fat layer of 30 the user, and each detector exposed to receive photons of the respective specific wavelength that have originated from each light source, and scattered from the localized tissue and passed back to the detectors through the subcutaneous fat layer and skin of the user, the support 35 member including conformable barrier means disposed

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between each light source and the detectors, the barrier means being of substance capable of conforming to the contour of the wearer and preventing light energy proceeding laterally in the region of the barrier means 5 from reaching the detectors.

Somewhat more generally, according to another aspect of the invention, an oximeter is provided for determining the oxygenation state of localized body tissue per se, constructed to be worn over a period of 10 activity by a user and comprising a flexible support member which supports, over the localized tissue of interest, at least a pair of spaced apart light sources, and intermediate thereof, at least a pair of wave length-specific light detectors (e.g., photo detectors), each 15 light source exposed to transmit wavelengths of both of the specific wavelengths toward the localized tissue of interest, and each detector exposed to receive photons of the respective specific wavelength that have originated from each light source, and scattered from the localized 20 tissue and passed back to the detectors.

Preferred embodiments of these aspects of the invention have one or more of the following features.

The light sources comprise broad spectrum CW light sources.

25 The light sources comprise tungsten filament lamps.

The oximeter includes control means for simultaneously flashing the light sources to enable each detector to pick up light energy at its specific 30 wavelength simultaneously from each light source.

Means are provided to flash the light sources at selected intervals unrelated to the interval of heart beats of the user.

According to another aspect of the invention, an 35 oximeter is provided comprising a flexible support member

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comprised of a molded-elastomeric backing member, the backing member mounting at least one light source means capable of producing one or more (e.g., two) selected wavelengths and oriented to direct the light to tissue of 5 a user and the backing member also mounting detector means capable of separately detecting energy at each of the wavelengths scattered by tissue of the user, integral elastomeric portions of the backing member defining a barrier exposed for conformable contact with an exposed 10 surface of the user, in position to prevent lateral movement of light in subcutaneous layers from the source means to the detector means.

According to another aspect of the invention, an oximeter is provided comprising a flexible support 15 member, the support member mounting at least one light source means capable of producing two selected wavelengths and oriented to direct the light to tissue of a user and the support member mounting detector means capable of separately detecting energy at each of the 20 wavelengths scattered by tissue of the user, the support member supporting a barrier member exposed for conformable contact with an exposed surface of the user in position to prevent lateral movement of light from the source means to the detector means, the barrier 25 comprising a member having an edge sized and positioned to indent skin and the flesh of the user thereby to intercept light migrating laterally in the subcutaneous fat layer and prevent such light from reaching said detector means.

30 Preferred embodiments of these aspects of the invention have one or more of the following features.

The barrier member is elastomeric, adapted to conform to the contour of the skin of the wearer.

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The flexible support member comprises a molded-elastomeric backing member and the barrier member is integral with the backing member.

The member defining the flesh-indenting edge is 5 about 0.5 cm thick in the region that engages the skin.

The barrier member comprises a rib-form member.

There are in series at least one (e.g., two) barrier members, one closely adjacent to the light source means and one closely adjacent to the detector means.

10 The support member mounts at least one (e.g., two) spaced-apart light sources and at least one (e.g., a pair) of detectors are disposed parallel to each other, disposed laterally relative to the line between the light sources and equal distance from each of the light 15 sources.

The light sources comprise broad spectrum CW light sources.

20 Electronic control circuitry for the light source and the detector means are provided in which the circuitry is disposed upon a miniature semiconductor chip carried by the support member.

25 Electronic control circuitry is provided comprised of entirely non-magnetic components enabling use of the device in conjunction with nuclear magnetic resonance imaging.

The oximeter is combined with a real-time readout device constructed to be worn by the user and having a display responsive to the oximeter disposed for viewing by the user.

30 The oximeter is associated with means securing it to an appendage of the user and the readout device is constructed to be worn by a user.

35 The oximeter is combined with radio frequency telemetry means for transmitting oximeter data on a real time basis to a station remote from the user or to a

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receiver in a readout device constructed to be worn by a user.

The oximeter includes electronic control circuitry for the light source and the detector means, the 5 circuitry disposed upon a miniature semiconductor chip carried by the support member in combination with radio frequency telemetry means controlled by the circuitry for transmitting oximeter data on a real time basis to a station remote from the user.

10 Means are provided for battery-operation of the oximeter and to record oximetry data in internal digital memory for subsequent display or data analysis on a computer.

The oximeter includes electronic control circuitry 15 for the light source and the detector means, the circuitry disposed upon a miniature semiconductor chip carried by the support member, and means for battery-operation of the oximeter and means to record oximetry data in internal digital memory for subsequent display or 20 data analysis on a computer.

According to still another device aspect of the invention, an oximeter is provided comprising a support mounting a light source and detector means at fixed spacing, and electronic control circuitry for the light 25 source and the detector means, the circuitry disposed upon a miniature semiconductor chip carried by the support member, the oximeter encapsulated in biocompatible, water impermeable material, the oximeter constructed and arranged for implantation under the skin 30 of a user for monitoring internal tissue oxygen trends.

The invention also features a number of methods. The method is provided of monitoring the derivative or rate of change of the time based curve representing detected change of tissue oxygen levels and blood volume

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and employing these rates as a quantitative standard of measurement of tissue oximetry.

The method is provided of assisting an aviator or other person engaged in activity that can subject the 5 person to high G-forces including providing to the person a comfortable oximeter sensor suitable to be worn about the head (e.g., either integrally in a helmet or helmet lining) and capable of responding to tissue oxygen level and blood volume of brain tissue on a real time basis, 10 employing the oximeter sensor to monitor oxygen level of brain tissue of the wearer as the wearer engages in the activity, comparing the monitored value to a standard and generating a signal, such as a warning or control signal, in the event the monitored level(s) violate(s) a pre- 15 established standard.

Preferably, the oximeter is constructed to monitor the trend of oxygen level in the brain, and means are provided to evaluate the rate of change being detected and using the rate of change as the control value and 20 alarm reference.

The method is provided of monitoring a person suspect of sleep apnea or sudden infant death syndrome including providing to the person a comfortable oximeter sensor capable of automatically responding to oxygen 25 level of the person while permitting the person to sleep, automatically monitoring the output of the oximeter by comparing it to a standard and generating a signal, such as a warning or control signal, in the event the monitored level violates a pre-established standard. 30 Preferably the oximeter sensor is taped comfortably to the head for monitoring. Also, preferably the method is used in conjunction with impedance pneumography (breathing rate measurement using chest-wall impedance) and/or EKG to provide an effective in-home apnea monitor 35 to alarm the patient or other individuals in the area so

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as to wake the patient and prevent hypoxic tissue damage during sleep.

The method is provided of monitoring the cerebral tissue oxygen rate of change as a means of triggering 5 alarm to awaken a subject in danger of infarct due to hypoxia.

The method is provided of monitoring both tissue oxygen level and blood volume in skin flaps such as are produced either by wound or surgery, as the flaps heal, 10 the separation between the source and the detector being established in relation to the thickness of the skin flap to ensure tissue of the flap per se is being monitored.

The method is provided of emergency monitoring of cerebral tissue oxygen level and blood volume in an 15 emergency care situation with the implantable device, in this case, preferably a stand-alone oximeter carried on a backing member with micro-circuitry to monitor the brain or other tissues in peril of damage due to hypoxia.

The method is provided of employing the device of 20 any of the configurations described above wherein the oxygen levels, blood volume and/or rate of change are measured in cancerous tissue to indicate the activity and viability of the tissue. Also preferably the method includes monitoring of the viability of a tumor following 25 treatment intended to wipe out the cancerous tissue.

Another aspect of the invention is a helmet into which is molded a tissue oximeter in position to engage the head of the wearer when the helmet is put on, the oximeter being of the NIR type, comprising light source 30 means for transmitting near infrared light into the head, detector means held in spaced position relative to the light source means for receiving light scattered by brain tissue and a barrier disposed to engage the head between the light source means and the detector means to prevent 35 light traveling laterally from the light source means

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from reaching the detector means. Preferably the oximeter has other features described above. In particular, preferably, the oximeter in the helmet includes control circuitry on a miniature chip and 5 preferably means are provided for determining the rate of change of oximetry readings and for comparing the rate of change to a standard and, e.g. producing an appropriate alarm and/or control signal.

Another feature of the invention is a tissue 10 oximeter comprising a support, a detector fixed to the support and a light source mounted in an adjustable manner to the support to enable selection of the spacing between light source and detector for adjusting the mean depth of tissue to which the oximeter responds.

15 Still another feature of the invention is a tissue oximeter in combination with means connected to receive tissue oxygen readings from the oximeter, and to determine the rate of change of the readings, the rate of change serving as a quantified indication of the state of 20 the charging metabolic process of the tissue.

Another feature of the invention is an oximeter as described, disposed on an endoscope, catheter or guidewire or the like for insertion via a body passage to internal tissue, and including means such as an 25 inflatable balloon to press the oximeter sensor against the localized tissue of interest. Another feature includes providing a water impermeable coating over the device for use in the presence of water.

Somewhat more generally, according to another 30 aspect of the invention, a cognition spectrophotometer system for transcranial examination of brain activity by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in the brain is provided. The cognition system comprises a light source 35 adapted to introduce electromagnetic radiation of a

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selected wavelength into the brain at an input port placed at a selected location on the exterior of the head; a detector adapted to detect, at a detection port placed at a selected location on the exterior of the  
5 head, radiation of the selected wavelength that has migrated in the brain; stimulation means adapted to cause stimulation of a brain activity while introducing the selected wavelength and while detecting radiation at the detection port; processing means adapted to process  
10 signals of the detected radiation that has migrated in the brain to create processed data, and evaluation means adapted to determine a characteristic of the brain activity by correlating the processed data with the caused stimulation of the brain activity.

15 Preferred embodiments of this aspect of the invention have one or more of the following features. Processing means adapted to process detected radiation that has migrated in the brain in the migration path between the input port and the output port being  
20 separated by a predetermined distance and being located at different locations on the exterior of the head.

The input port and the output port are located on the frontal bone, parietal bone, temporal bone or occipital bone, wherein the input port and the output  
25 port being separated by a predetermined distance in order to localize the migration of the radiation to a selected region of the brain. The predetermined distance can be 4 centimeters.

The system can also have a second light source  
30 adapted to introduce electromagnetic radiation of the selected wavelength into the brain at a second input port placed at a second selected location on the exterior of the head; a second detector adapted to detect, at a second detection port placed at a selected location on  
35 the exterior of the head, radiation of the selected

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wavelength that has migrated along the migration path in the brain from the second input port to the second detection port, and processing means adapted to process signals of the detected radiation that has migrated in 5 the brain from the second input port to the second detection port to create second processed data, wherein the evaluation means determine the characteristic of the brain activity by correlating both first mentioned and the second processed data with the caused stimulation of 10 the brain.

This system is adapted to introduce the radiation simultaneously at the two input ports or sequentially at the first input port and detected at the first detection port, and subsequently introduce the radiation at the 15 second input port and detected at the second detection port.

According to another aspect of the invention a cognition spectrophotometer system for transcranial examination of brain activity by measuring changes in 20 electromagnetic radiation scattered and absorbed in a migration path in the brain is provided. The cognition system comprises a first light source and a second light source adapted to introduce electromagnetic radiation of a selected wavelength into the brain simultaneously at a 25 first input port and at a second input port; the first input port and the second input port being placed at a first selected location and a second selected location on the exterior of the head, respectively; a first detector and a second detector adapted to detect simultaneously, 30 at a first detection port placed at a selected location on the exterior of the head, radiation that has migrated in the brain from the first input port to the first detection port and, at a second detection port placed at second selected location on the exterior of the head, 35 radiation that has migrated in the brain from the second

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input port to the second detection port; stimulation means adapted to cause stimulation of a brain activity while introducing the radiation at the first and second input ports and while detecting radiation at the first 5 and second detection ports; processing means adapted to process signals of the detected radiation that has migrated in the brain to create processed data; and evaluation means adapted to determine a characteristic of the brain activity by correlating the processed data to 10 the caused stimulation of the brain activity.

Preferred embodiments of this aspect of the invention have one or more of the following features. The system has the first input port and the first output port located on one parietal bone (or temporal bone), 15 separated by a predetermined distance, in order to localize migration of the radiation in a selected region of the respective hemisphere of the brain, and the second input port and the second output port located on the other parietal bone (or temporal bone), separated by a 20 predetermined distance, in order to localize migration of the radiation in a selected region of the other hemisphere of the brain.

The system's processing means are further adapted to compare electromagnetic radiation detected at the 25 first and second detection ports to create processed data representing a differential signal.

The processing of the detected radiation can comprise Fourier transformation.

The stimulation means are adapted to cause visual 30 stimulation, acoustic stimulation, or sensorimotor stimulation.

The evaluation means can be adapted to examine pathophysiological properties of the brain tissue or cognitive function of a selected region of the brain

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based on correlation between the processed data and the caused stimulation of the brain activity.

The system's first and second light sources are tungsten lamps or light emitting diodes. The first or 5 second detectors are silicon diodes or light-to-frequency convertors each with an interference filter adapted to detect the radiation of the selected wavelength.

The processing means comprise differential counter adapted to register differential signals received from 10 the light-to-frequency convertors, clocking means adapted to route signals of the detected radiation from the light-to-frequency convertors to the differential counter, a frequency-to-voltage converter adapted to convert signals from the differential counter and/or a 15 fast Fourier transformer adapted to process differential signal from the frequency-to-voltage converter.

The evaluation means comprise a storage oscilloscope adapted to analyze the Fourier transformed differential signal of the fast Fourier transformer, 20 and/or computational means adapted to analyze the differential signal.

According to another aspect of the invention a cognition spectrophotometer system for transcranial examination of brain activity by measuring changes in 25 light scattered and absorbed in a migration path in the brain is provided. The system comprises the above-described oximeter, stimulation means adapted to cause stimulation of a brain activity while introducing the light using the light source and while detecting the 30 light that migrated in the localized tissue of interest of the brain, processing means adapted to process signals of the detected light that has migrated in the brain to create processed data, and evaluation means adapted to determine a characteristic of the brain activity by

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correlating the processed data to the caused stimulation of the brain activity.

According to another aspect, the invented system enables examination of a tissue of an organ by measuring 5 changes in electromagnetic radiation scattered and absorbed in a migration path in the organ. The examination is performed by the steps of (a) introducing electromagnetic radiation of a selected wavelength into the organ simultaneously at a first input port and at a 10 second input port; the first input port being placed at a first selected location, and a second selected location, respectively; (b) detecting simultaneously, at a first detection port placed at a selected location on the exterior of the head, radiation that has migrated in the 15 organ from the first input port to the first detection port and, at a second detection port placed at second selected location on the exterior of the organ, radiation that has migrated in the brain from the second input port to the second detection port; (c) processing signals 20 corresponding to radiation detected at the first and second detection port that have migrated in the brain to create first and second processed data, respectively; and (d) determining a selected property of the organ tissues by correlating the processed first and second data.

25 The organ can be the brain, breast, limb, etc. If the organ is the brain, then the first input port and the first output port are located on one parietal bone (or temporal bone), separated by a predetermined distance, in order to localize migration of the radiation in a 30 selected region of the respective hemisphere of the brain, and the second input port and second output port are located on the other parietal bone (or temporal bone), separated by a predetermined distance, in order to localize migration of the radiation in a selected region 35 of the other hemisphere of the brain.

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Brief Description of the Drawings

Figure 1 is a depiction of a preferred configuration of an embodiment of the present invention.

5 Figure 2 is a partially diagrammatic, partially schematic representation of a preferred embodiment detector.

Figure 3 illustrates another preferred configuration of an embodiment of the present invention.

10 Figure 4 is a partially diagrammatic, partially schematic representation of an alternate preferred embodiment detector.

Figure 5 is a plan view of another preferred embodiment.

15 Figure 6a is a plan view of the oximeter sensor of Figure 5.

Figure 6b is a longitudinal sideview of the oximeter sensor of Figure 6a.

Figure 6c is a longitudinal cross-sectional view taken on line 6c of Figure 6a;

20 Figure 7 is a transverse cross-sectional view of a oximeter sensor according to the invention in place upon the flesh of a wearer;

Figures 8a, 8b and 8c are plan views of other preferred embodiments of the oximeter sensor;

25 Figure 9a is a plan view of an implantable oximeter sensor according to the invention;

Figure 9b is a longitudinal sideview of the oximeter of Figure 9a;

30 Figure 9c is a cross-sectional view taken on line 9c of Figure 9a;

Figure 10 is a block diagram of an analog version of the control system for the oximeter of the previous figures;

35 Figure 10a is a schematic representation of the oximeter control system shown in figure 10;

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Figure 10b is a section of the schematic representation shown in figure 10a;

Figure 11 is a block diagram of a digital version of the control circuit of the oximeter of the previous 5 figures;

Figure 12 is a software flow diagram of the software used with the circuitry of Figure 11;

Figure 13 is a front of a helmet according to the invention;

10 Figure 14 shows an endoscopic oximeter according to the invention;

Figure 15 is a block diagram of a low frequency cognition spectrophotometer;

15 Figure 16 illustrates the response of the Fourier transform oscilloscope of the cognition spectrophotometer, shown in Figure 15, to 300  $\mu$ V peak-to-peak square wave (top trace) and 225  $\mu$ V sine wave (lower trace);

Figure 17 illustrates the response of the DC 20 amplifier to a square wave;

Figure 18 shows frequency analyses of optical signals of subject U obtained by the cognition spectrophotometer of Figure 15;

25 Figure 19 shows frequency analyses of optical signals of subject B obtained by the cognition spectrophotometer of Figure 15;

Figure 20 shows frequency analyses of optical signals of subject U at rest obtained by the cognition spectrophotometer of Figure 15;

30 Figure 21 shows a histogram display of the distribution of frequencies obtained by the cognition spectrophotometer of Figure 15;

Figure 21a shows a histogram display of the distribution of energy (area) in the peaks obtained by 35 the cognition spectrophotometer of Figure 15;

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Figure 22 is a block diagram of a fast lateralization detector of the cognition spectrophotometer of Figure 15;

Figure 23 is a block diagram of a low frequency 5 lateralization detector of the cognition spectrophotometer of Figure 15.

#### Detailed Description

A preferred embodiment of the apparatus of the present invention is illustrated in Figure 2. In this 10 embodiment an electro-optical pickoff detector unit 10 is worn on the leg of the exercising subject 50. It is preferred that the weight of the detector be kept to a minimum so that hindrance to a competing athlete is negligible. In a preferred embodiment, the detector will 15 be housed in a flexible array constructed from a suitable non-irritating, lightweight material.

Power is provided to the detector unit 10 from a replaceable battery pack 30. The replaceable power pack 30 is preferably designed to be of minimal dimensions and 20 weight. Most preferably, the battery pack 30 would be designed to last only for the duration of the activity, e.g., several minutes of sprinting, several hours for a marathon runner, etc. In competitive sports 25 applications, the life of the battery pack is preferably based upon the interval between substitutions or other interruptions between periods of competition.

The embodiment illustrated in Figure 1 further comprises an arm indicator 40, which is preferably worn on the arm in the manner of a wristwatch. The arm 30 indicator 40 displays the percentage of deoxyhemoglobin (%Hb) as a measure of the subject's metabolic state. As seen in Figure 1A, such a display may comprise a simple readout of this information, such as a bar graph. Alternatively, the information displayed may be placed on

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a time scale, to graphically illustrate the change in %Hb concentration over the course of the activity, as illustrated by Figure 1B. In a most preferred embodiment, the graphic displays illustrated by Figures 5 1A and 1B are comprised of liquid crystal displays (LCD's), although other electrical or electronic display means may also be used. The amplitude interval of this embodiment is preferably divided into 6-10 levels, each covering a portion of the designated %Hb scale.

10 It will be appreciated that the range of the %Hb scale may be adjusted depending upon the range expected to occur during the activity. Since the precision of the present invention is limited by that of the indicator, the range which is displayed is an important variable

15 parameter. In the most accurate embodiment of the present invention, with the endpoints of the %Hb scale set at 20% and 40%, the apparatus would have an accuracy of about 6%, which is about the limit of precision which can be obtained from a moving limb. One of ordinary

20 skill will realize that the gain of the apparatus is preset, depending upon the intensity of the activity expected. In a most preferred embodiment, a button placed on the arm indicator 40 allows the gain to be set.

Referring now to Figure 2, there is illustrated a 25 partially schematic, partially diagrammatic representation of a preferred embodiment of a circuit which comprises the optical pickoff component of a DC tissue spectrophotometer detector 10 contemplated for use in the system of the present invention. The detector 10 30 is shown for illustrative purposes mounted against a skin surface 25 of a subject. In a typical configuration, the detector is mounted against either large, homogeneous muscles, such as the gastrocnemius or the quadriceps or against the forehead of an adult. Two lamps 12,14 and 35 two detectors 16,18 are contained in a flexible

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waterproof array. Also contained in the array is an opaque specular barrier, which is a concentric ring of material 11 between the lamps 12,14 and the detectors 16,18 which acts as a barrier zone to light of a specified wavelength. Most preferably, the material which comprises the barrier zone will not only be opaque to light within a specified region, but will further act as an absorber as well. The configuration of dual wavelength light sources combined with a barrier zone is disclosed in "Optical Coupling System for Use in Monitoring Oxygenation State Within Living Tissue," Application No.266,116; filed November 2, 1988, which is incorporated herein by reference, as noted above.

Thus, superficial light rays from the skin are, in effect, blocked by the opaque barrier 11 from entering the detectors 16,18. This blocking action by the barrier 11 of these superficial rays enables the system to determine the oxygenation state of hemoglobin within the muscle rather than at the skin surface. The rays that migrate deep within the tissue are received by the detectors 16,18. The light rays that migrate superficially "escape" through the skin surface and will be absorbed by the opaque barrier 11. When, for example, a 760 nm impulse is applied, the deoxygenated hemoglobin (Hb) within the muscle is detected and when an 800 nm signal is applied, the oxygenated and deoxygenated hemoglobin ( $\text{HbO}_2$  and Hb) within the tissue region are detected. The system is able to ignore the oxygenation state at the skin surface and determine that within the tissue.

The lamps 12,14 may be, for example, 1/2 W flashlight bulbs that are periodically illuminated in the NR region. The lamps are provided with cutoff filters 13,15 so that only energy of a specified wavelength illuminates the tissue. The silicon diode detectors

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16,18 are sensitive to  $760 \pm 20$  nm and  $800 \pm 20$  nm (or  $850 \pm 20$  nm) wavelengths, respectively.

In a preferred embodiment, the lamps 12,14 are light emitting diode (LED) sources, which emit light 5 having a wavelength of about  $760 \pm 150$  nanometers and about  $800 \pm 150$  nanometers (or  $850 \pm 150$  nanometers), respectively. In either embodiment, the lamps are flashed or pulsed at a predetermined repetition rate. The repetition rate of sampling, i.e., the rate at which 10 the lamps are flashed determines the rate at which data may be collected. Thus, for a long distance runner, the lamps are flashed slowly; the output is commensurately changed for a sprinter, the lamps flashed rapidly to produce sufficient data to evaluate an exercise having a 15 duration on the order of seconds. The selection of LEDs as sources of electromagnetic radiation provides a further advantage, since these sources produce a signal-to-noise ratio (S/N) approximately one order of magnitude greater than previously disclosed optical coupling 20 systems using optical light fiber sources.

Referring now to Figure 4, an alternate embodiment of a circuit for use with the present invention is illustrated. In this case a single detector 17 responding to separate light flashes collects and 25 transmits signals to an amplifier 24, which has bipolar outputs that are connected intermittently to an integrator 27 by a switch 25. Another switch 26 adjusts the relative duration of the two light pulses to equalize the two signals. One of ordinary skill will understand 30 that those portions of Figure 2 and Figure 4 having the same reference numerals perform substantially similar functions. Many details of the particular circuits comprising the present invention need not be set forth with particularity as they are well known or will be 35 obvious to those of ordinary skill.

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Referring to Figure 2, it can be seen that the detectors 16,18 are also protected by a transmitting filter 19 pressed against the skin to minimize the effect of background light. The filter 19 may be comprised of a 5 separate member, a coating or integrated into the housing of the circuit. The DC output of each of the detectors 16,18 is timeshared into its respective differential amplifier 20,22. The amplifiers are connected in opposite polarity, one non-inverting, the other 10 inverting. The dwell time of the switch 23 connecting the amplifiers 20,22 is adjusted to equalize the response of the two signals by appropriate circuitry 28. The signal from the integrator is coupled to a recorder (not illustrated). As shown in Figure 4, the signal from the 15 800 nm lamp 12 may be simultaneously employed to vary the gain of the amplifier 24 so as to correct the signals for changes of blood volume and to produce the ratio of the two signals, and thus maintaining constant sensitivity for difference detection. One of ordinary skill will 20 appreciate that a similar gain compensation circuit can be incorporated into the circuitry of the 800 nm detector amplifier 22, shown in Figure 2. Whether incorporated into the circuits of Figure 2 or Figure 4, the 800 nm signal is also coupled to a second recorder channel to 25 collect data reflecting total absorption or blood volume.

Another configuration of the present invention is illustrated in Figure 3. In this embodiment, a radio-linked telemetry system comprised of a transmitter 60 attached to the subject and a receiver 62, allows the 30 remote monitoring of the subject. A supervisor, coach, or clinician is thereby enabled to monitor the performance of the subject. The data display is remote, one of ordinary skill will appreciate that the displays utilized may be similar to those illustrated in Figures 35 1A and 1B, or may be more complex, displaying data using

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various scales, time overlays, colors, etc. In a most preferred embodiment the telemetry signal would be carried on the 220-400 MHz band, using a transmitter in the 100 MW range.

- 5        The configuration illustrated by Figure 3 allows the present invention to monitor athletes in competition or workers and military/space personnel located in remote locations. For example, the apparatus of the present invention may be used in training to determine the
- 10      duration of peak performance and the appropriate times for the substitution of fresh players or other adjustments. This configuration would also be preferred for monitoring the metabolic condition of an animal such as a racehorse, racing dog, or any animal whose metabolic
- 15      condition is being studied for clinical or other purposes. A "postage stamp" oximeter may be provided for, e.g., emergency use, where the oximeter is held to the subject by an adhesive pad positioned peripherally around the device.
- 20      In any of the embodiments of the present invention, it is preferred that the data be integrated over at least about ten seconds to smooth out irregularities which normally occur in the concentration of deoxyhemoglobin during exercise. However, it will be
- 25      understood that the period integration can be varied, depending upon the duration of the activity being monitored.

Although manual balancing of the apparatus of the present invention is required, in a preferred embodiment, 30 the balancing is accomplished by depressing a button, which will normalize the output of the two wavelengths. Automatic balancing performed by an intelligent gain control CPU is also envisioned.

Another preferred embodiment of the oximeter is 35 shown in Figures 5 and 6a-6c. A rubber-backing member

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101, provides support for two lamps 100 spaced equi-distant from two detectors 102 also mounted on backing member 106. The backing member is formed of an opaque, e.g., black, silicone rubber of suitable durometer to 5 enable it to conform to the curvature of the subject part of the human body to which it is applied. For this embodiment, which may be as long ( $L_1$ ) as e.g., 12, especially 8 centimeters, flexure configurations 106 are provided. Light barrier members 103, 104 serve to 10 depress the subcutaneous fat layer and thereby reduce light interference directly between the light sources 100, located at input ports, and the detectors 102, located at detection ports, see description below regarding Figure 7. Behind the detectors 102 of Figure 15 6a, as shown in Figure 6c, housing 107, defined by the rubber wall, contains the supporting circuitry for these lamps and detectors. As shown in Figure 6c, narrow band optical filter 110, located at the detection port, lies over photodetector 111, which lies over circuitry 108. 20 Depth D is typically 2 cm. Wiring harness 115 carries power to the lamp.

On the rubber supporting member 101 there are a number of integral raised members 103, 104, 105 and 106. Raised rib 105, which extends about the perimeter, both 25 prevents external light from interfering with the reading and serves to support comfortably the backing member 101 on the subject. Rib 104 extending laterally, adjacent the lamp, and disposed across the line projected between the lamp 100 and the detectors 102, serves as a second 30 light barrier to prevent interfering light transmission between light source 101 and detectors 102. Rib 103 closely surrounds the detectors, and serves as a primary eliminator of environmental light interference, and also serves to absorb light migrating along subcutaneous fat 35 and other subsurface interposed layers, etc. All of

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these ribs are on the order of 1/2 centimeter high and 1/2 centimeter thick. Their outside flesh-engaging edges are rounded for comfort to the wearer. The supporting member 101 and its associated ribs are manufactured in 5 one piece of molded rubber. A suitable mold is provided and black silicone rubber is poured into the mold, cured and dried, leaving the subsequent rubber backing 101 with integral ribs and structures. Suitable mounting sites are provided in the backing into which the detectors 102 10 and the lamp 100 are mounted during final manufacturing. The backing member for the oximeter sensor of Figures 6a-6c has width, W, length, L1, and depth, D, which may be varied depending upon the application. L2 represents the spacing between light source 100 and the center of 15 detectors 102. Sensors with dimension (L<sub>2</sub>) from one centimeter to four or five centimeters with corresponding changes in L1 and W are appropriate. One centimeter separation L2 is useful for muscles of very shallow depth while L2 of four or five centimeters is useful for deeper 20 tissue penetration, for example for the brain or other organs.

Small L2 spacings of as low as one centimeter are also appropriate for monitoring tissue flaps, though the best configuration of the sensor for flaps is that shown 25 in Figure 8c, described below, because flaps are of varying thickness and the adjustability of the device of Figure 8c enables L<sub>2</sub> adjustment proportional to the thickness of the flap. It will also be realized that monitoring may be achieved through wound dressings, 30 bandages, etc.

In the currently preferred embodiment, the light sources 100 are lamps having tungsten filaments, are broad band light sources which eliminating the problem of matching the light sources to the detector filters.

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Each detector is comprised of interference filter 110 which blocks out all light except for that which is desired, each of two detectors having a separate wavelength of interest. At this time 760 nm and 850 nm 5 are preferred, although one can envision that changing, depending upon the application. Beneath the filter is a photosensitive detector which picks up the light and transduces it to an electrical signal which is amplified in the circuit 108 and later transmitted to the control 10 circuitry represented in either Figure 10 or 11.

In the presently preferred embodiment, the interference filter is manufactured by Omega, Inc., and the photodiode beneath it is Part No. F1227-66BR, available from Hamamatsu, having a large sensitive area 15 for favorable signal to noise ratio and an NIR wavelength sensitivity. The sensitive area is approximately 6 millimeters squared.

In the present embodiment the filter and detector are epoxied together around and an electronic shield 115 20 surrounds the diode/filter pair 110 and 111. This surrounding electronic shield eliminates or reduces extraneous electronic interference. It is presently preferred to form this shield of copper in the form of a windowed box which surrounds the detector filter pair.

Once the two separate filter diode pairs are 25 constructed, they are soldered together and then mounted directly to the circuit board 108. Connected also to circuit board 108 is an ultra low noise operational amplifier with high gain, which converts the current 30 signal from the diodes to a voltage applicable to the control circuitry of Figures 10 or 11. The circuit board 108 can be connected via either telemetry or cabling to the oximetry system 99 of Figure 5, which contains the circuitry shown in Figures 10 or 11. Power supply for 35 the amplifier of 108 is supplied by the oximetry system

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99 where a cable connection is employed. In other embodiments, a battery is provided for operating the oximeter sensor along with the telemetry system, to be described below in connection with an implantable 5 embodiment.

Referring now to Figure 7, the preferred embodiment of Figures 6a-6c is shown diagrammatically as it is placed upon the skin of a subject. The edges of the upstanding rib-form barrier members serve to 10 concentrate pressure upon the skin, depressing the skin layer and the underlying fat layer. The barriers 103 and 104 serve to prevent light from migrating directly between the source 100 and the detectors 102 and because the barriers are placed with pressure upon the surface of 15 the skin, they serve to reduce the area of the fat through which light can pass directly. If one were to imagine the situation without a barrier, one would see light passing almost directly between the source and the photodiodes, the fat layer serving, effectively as a 20 light guide. The absorbing ribs reduce this noise effect. Light which is emitted by the sources 100 enters the skin directly beneath the source, passes through the fat to the underlying tissue, migrates through the tissue, is absorbed, scattered, and eventually is 25 received by the photodiode. The migration path has been described in prior art as a banana-shaped path which is due to the photon migration between the source and the detector. "Banana-shaped" is a mean representation of the photon path, whereas the actual migration path 30 constitutes many scattering changes of direction of the photons as they course between the light source, located at the input port, and the photodiode, located at the detection port.

Figure 8a-8c show alternate preferred embodiments 35 of the oximetry sensor.

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The embodiment of Figure 8a is useful for muscle. It is shown here as a comparison to Figures 6a-6c, wherein the overall length L1 and the overall width W depends upon the application and L2 as in Figures 6a-6c  
5 can vary dependent upon the application from one centimeter or less to five centimeters or more.

The overall length L1 is determined chiefly as a result of the source 100 to detector 102 spacings L2. The spacing determines the depth of penetration of the  
10 light which is scattered and migrated through the tissue. The farther the source is from the detector, the deeper the mean penetration. So for shallow penetrations, one would envision a short L2 and thereby L1. The penetration desired depends upon the muscle of interest.  
15 For a large muscle, for example, in the thighs or the calf, which tend to be fairly large, one needs a substantial separation to both (a) penetrate the thicker fat layer and (b) to sense deeper into the larger muscle.

For such muscles, a common dimension for L2 would  
20 be 3 to 5 centimeters and L1 would thereby be 7 to 11 centimeters.

The width of the sensor is chiefly dependent upon the size of the detectors 102. In the configuration of the presently preferred embodiment wherein each detector  
25 has a photosensitive area of approximately 6 millimeters squared, the width is dependent almost entirely upon those two dimensions. As the photodetectors reduce in dimension width W decreases.

The larger photodetector units provide better  
30 signal to noise ratio and thereby enable more accurate representation of the oxygenation state of the tissue. As improvements in technology occur and better photodetectors and initial amplification circuitry are developed, the detector size will decrease, with  
35 consequent decrease in W.

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As with Figure 6a-6c, the supporting member 101 of Figure 8a carries numerous rib-form barriers. In this case barriers 103, 104 and 105 serve both support and light reduction functions. Perimeter barrier 105 in this 5 case completely surrounds the light source and detector grouping. Between the light source and barrier 103, is barrier 104 on opposite sides of the detectors. Barrier 104, as previously mentioned, serves to reduce light as it travels between source and detector in the 10 subcutaneous layer.

The embodiment of Figure 8b represents an alternate to that of Figure 8a wherein the dimensions of Figure 6a are significantly reduced to achieve a smaller probe. In addition to the backing member 101 being 15 reduced in size, in Figure 8b, barrier 104 has been eliminated and barrier 103 serves as the primary and only eliminator of both external light and interference between source 100 and detector 102. The typical dimensions for L2 of Figure 8b would be 3 centimeters or 20 less, L1 being 6 centimeters maximum or less. In comparison, the minimum size for the embodiment of figures 8a and 6a-6c of L2 would be 3 centimeters or greater.

The embodiment pictured in Figure 8b is suitable 25 to be used for example in neonate applications where the desired tissue volume is extremely small and one needs a small probe. It would also be used for very shallow depth muscle and for example, skin flap measurements where skin flaps are created either by surgery or by 30 wound. The sensor is placed over the skin flap to determine the health of that flap as it heals.

The smaller sensor sizes improve the flexibility of the device to correspond to perhaps smaller target muscles and smaller regions of interest.

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Referring to Figure 8c, a similar embodiment to that of Figure 6a-6C is shown, but having a light source track 109 to enable variable spacing between the light source 100 and detector. Barrier 103 has been omitted in 5 favor of allowing for user settable variations of L2. L2 may be varied between for example 2 centimeters to say 5 centimeters depending upon the application. This may be used for skin flap work in determining the health of a skin flap as described above, with the distance L2 set in 10 accordance with measurement of the thickness of the skin flap.

For this adjustability, a slide mechanism is employed in manner to keep L2 equal on both sides, in dependent motion such that as the spacing of one varies, 15 the spacing of the other will also change.

The embodiments of Figures 5-8 share the desirable features of a parallel pair of detectors 102, side-by-side extending across the line between the light source. By simultaneous flashing of both lamps each detector 20 receives photons at its wavelength from both lamps, simultaneously.

Figure 9 shows another preferred embodiment of the tissue oximeter sensor, in the form of an implantable probe. To further reduce size, one of the light sources 25 100 is omitted. As in Figure 8b, light barrier 104 is omitted. The lone barrier in this case 117 serves to reduce direct light interference.

As previously mentioned, backing member 101 holds in fixed relation the light source 100 and the detectors 30 102. The length L1 is solely dependent upon a single L2 between the single source and the dual detectors. The spacing depends chiefly upon the muscle location internally of the organ which is being studied. As previously mentioned, from 1/2 centimeter or 1 centimeter 35 to 5 centimeters may be appropriate, depending upon the

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application. Applications envisioned are horse muscle studies.

For application, the physician makes an incision in the skin and slips the oximeter sensor underneath the 5 skin and cutaneous fat layer. There are suture points 113, e.g., biocompatible webbing, surrounding the backing member 101. A coating over the entire sensor is comprised of a biocompatible base material 112, which protects the circuitry from the human system, and 10 protects the human from the invasive nature of the circuitry.

The thickness of the device is of the order of 1 to 2 centimeters maximum. That depth dimension will diminish as technology changes. In Figure 9c the 15 supporting circuitry is shown. As previously described, the filter/photodiode pair 110, 111 is disposed above the circuit 108. In addition to receiving and amplifying the signal, the circuit shown here is responsible for telemetric communication of the signal to a receiver 20 outside of the body. A battery 114 powers that circuitry.

By employing a radio signal to transmit the information from within the body to a receiver outside the body there is no need for wires and the like 25 puncturing the skin.

Referring to Figure 10, one embodiment of the circuitry for driving the device is shown. (Schematic diagram of the embodiment of Figure 10 is shown in Figure 10a.) This is an analog circuit wherein the signal from 30 photodetectors 118 and 119 is amplified by amplifiers 120 and sent to three manipulative circuits that take the difference, the sum and the derivative of the signal. The difference 123, as described above, simply subtracts 760 nm minus 850 nm to obtain a signal representing 35 deoxygenation.

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The sum circuit 124 takes a weighted sum of the 760 nm and 850 nm signals, weighting being chosen appropriate to the fact that the signal variation due to oxygenation or deoxygenation is greater for 760 nm than 5 it is for 850 nm. Because these contrabestic wavelengths tend to cancel the signal due to the difference in oxygenation, the sum shows independent of the difference and is taken as representative of the blood volume changes in the tissue.

10 The derivative circuit 125 takes the simple derivative to show the rate of change of both of the signals. This is useful, as described above, to trigger alarm circuitry based upon established standards, wherein the higher the rate of the change, and the more sustained 15 that rate of change, the more potentially dangerous the rate of change. This is useful, as mentioned, for example in monitoring aviators for possible black-out conditions and for apnea.

10 The outputs of these units 123, 124 and 125 are applied to the control circuit which controls where the signals are directed and how they are displayed and/or sent to a computer. The control circuit may be simply embodied as a switch to switch the output to an LCD display, for example. The analog signal from control 25 circuit can be digitized in the display unit 127 and displayed as a digital number. Additionally it can be digitized and sent to a computer or sent in analog form to a computer for digitization.

10 The oscillator 121 is an independent source for determining the frequency of lamp flashing. Lamps flash at frequency of 1/2 Hz or 2 flashes per second or greater. This frequency may be independent of heart rate or any other external factor and is set externally by the user, and may be dependent upon application as mentioned 35 earlier. For example, during exercise, the frequency

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chosen for the lamp will depend upon the frequency of the exercise, such as the revolutions per minute on a bicycle. If one is expected to encounter a slow change in oxygenation due to the nature of the exercise or the 5 muscle of interest, one can employ a fairly low flashing rate. There is no need for high resolution measure of the rate of change as is required in pulse oximetry.

The lamp rate is tied to the control circuit. The oscillator establishes the timing for the sum and 10 difference circuits because the sum, difference and derivative circuits need to be synchronous. In operation, the lamp flashes, the signal is picked up by the photodetectors and while the lamps are on, the difference, sum and derivative are calculated and are 15 thereby stored in the appropriate memories, and via the control circuit can be directed to the display and to the computer.

The derivative system is the basis of the alarm system. Output from the derivative is compared to a 20 standard within the alarm circuitry, which then determines if there is, for example, a normal rate of change, represented say by a green light, a cautionary rate of change, which may be represented by a yellow light, and a fairly rapid and/or sustained rate of 25 change, which would be for example shown by a red light, an alarm or a buzzer or the like, which would alarm both the wearer or act remotely for example to warn the parents of a neonate in the case of SIDS (Sudden Infant Death Syndrome).

30 The embodiment shown in Figure 10a enables correction for the dark current/noise that comprises background light, DC offset of the operational amplifiers, photodiode dark current, temperature effects on the outputs of individual components and variations 35 due to changing environment. The dark current/noise

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correction is explained on the circuit of Figure 10b which is a section on the analog circuit, shown in Figure 10a. The oximeter (Figure 10) performs data acquisition in four steps which are synchronized by an internal oscillator. In the first step, the lamps are off. The output is directed to an integrator 154 and integration capacitor 156 is charged to the dark level voltage. In the second step, the lamps are turned on. The preamplifier output that corresponds to the intensity of the detected light is directed to integrator 154 in a way to charge capacitor 156 with current of polarity opposite to the polarity of the charging current in the first step. This is achieved using appropriate ON/OFF combination of switches S1 and S2. The voltage of capacitor 156 is charging to a value which, at the end of this step, represents the total signal minus the dark level noise signal. In the third step, both switches S1 and S2 are turned OFF to disconnect both the positive unity gain and the negative unity gain operational amplifiers (150 and 152). Then, the output of integrator A is moved via switch S3 to a hold circuit 158 which also functions as a low pass filter. This output is the detected signal at one wavelength corrected for the background noise. In the fourth step, the switches S1, S2 and S3 are open and switch S4 is closed in order to discharge capacitor 156 through a 47K resistor. At this point, the circuit of integrator 154 is reset to zero and ready for the first step.

In another preferred embodiment, digital version 30 of the circuitry depicted in Figure 11, the identical photodetectors 118 and 119 and similar amplifiers output signal to an analog to digital conversion system 128 and to a derivative circuit 124. The derivative circuit outputs signal to the analog digital converter, in this 35 case for evaluation by the central processing unit, CPU,

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or microprocessor 129. Software, shown in Figure 12, controls the system of data collection and lamp frequency 122 as well as the storing of data, interfacing with external computers and displaying or telemetrically 5 communicating this information. The heart of this circuit is the central processing unit driven by software which collects data, stores it, displays it and sounds alarm if necessary.

Figure 12 shows the software. Initialization of 10 the system 140 takes place whereby the analog and digital system is set up and configured properly. The digital memory, communication and telemetry are configured as in Figure 11. Secondly the device calibration takes place such that the gain of the amplifiers is set 15 electronically by software. The gain of the amplifiers is set to an acceptable range so that digitization can take place accurately, as well as other small internal routines to determine whether the derivative is working properly or not. In the case that the calibration cannot 20 take place, the program will stop and alarm the user. The alarm 134 represents "not working properly, please reset", etc. After calibration is completed successfully, data collection is begun. Data collection is taken in a loop format starting with 142. It starts 25 with turning the lamp on, and sampling the signal, 143. Approximately 500 points of data are taken in rapid succession over approximately 1/2 second sampling interval or less. That data is accumulated, then the lamp is turned off after a delay period, which is set by 30 the user and by the software. The samples are collected and then averaged at 144. This average is then used at 145 to calculate the sum, difference and derivative. In this case the calculated derivative serves as a redundant comparison with the analog derivative calculated in 125 35 of Figure 11. In addition to the averaging of 760 and

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850 nm, the derivative signal is also averaged and sampled in the same way, for example with 500 points. By this means a calculated derivative as well as a sample derivative are obtained which are compared to provide a 5 much more repeatable and reliable result for an alarm.

The data after it has been manipulated in 145 will be stored, appropriately transmitted and/or displayed. In addition the alarm is set off if necessary at this point. Then finally an independent timer or delay would 10 be introduced. The processor is delayed for a set period to obtain desired lampflash/data collections frequency.

The sequence is thus: lamp on, collect sample data, lamp off, collect noise data, average sample, calculate sum, difference and derivative, then transmit, 15 display etc., wait if necessary, and then turn on the lamp again and repeat the whole procedure.

Referring to Figure 11, dark current/noise correction in this analog system is accomplished by sequencing the data collection using the microcontroller. 20 The data is collected in two sequencing steps. One step has light on and the other step has light off. The data collected with the light off represents the dark current. The data collected in the first and in the second cycle are digitally subtracted in order to obtain intensity 25 data corrected for the dark current noise.

Referring now to Fig. 13, a helmet 170 is shown having a tissue oximeter 172 molded at a position to snugly engage the head of the wearer when the helmet is put on, typically at a position free of body hair, e.g., 30 at the forehead above the eyebrow. The oximeter is of the type, e.g., as described in Fig. 8b, having a source for transmitting NIR light, a detector to receive the light scattered from tissue such as brain tissue and a barrier to engage the head between the light source and 35 the detector to prevent light traveling laterally between

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source and detector through subcutaneous layers.

Preferably, the oximeter in the helmet includes a control circuitry on a miniature chip and preferably circuitry and/or software are provided for determining the rate of

5 change of oximetry readings and for comparing the rate of change to a standard.

Referring now to Figs. 14a-14b, an oximeter 180 is disposed on a catheter 150 (e.g., an endoscopic catheter), having an inflatable balloon 160 and endoscope 10 optics 190. The oximeter 180 is preferably of the design illustrated in Fig. 7, and is molded or otherwise attached to the outer surface of the balloon.

Controlling and detected signals may be passed to and received from the oximeter by wires passing through the 15 balloon and a lumen within the catheter or by transmission from the oximeter to a receiver outside the body by telemetry as discussed, e.g., with respect to Fig. 9. In operation, the catheter, with the balloon deflated, is passed through a body lumen to the position

20 of interest, guided for example, by fluorimetry or by endoscopic viewing. The balloon is then inflated to press the oximeter against the tissue of interest and measurements taken as described above. The technique and apparatus may be applied, for example, to body lumens 25 such as the GI tract (e.g., for measurements of GI tract wall ischemia or hypoxia as determined to be a preliminary indicator of multiple organ failure) or to blood vessels, employing an angiographic catheter for analysis and treatment of occlusions, etc. Still other

30 embodiments are possible. For example, a "postage stamp" oximeter may be provided, e.g., for emergency use (self-contained system with alarm as discussed), where the oximeter is held to the subject by an adhesive pad, positioned peripherally around the device. Another 35 embodiment includes providing a water impermeable coating

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about the device for applications in the presence of water, e.g., for scuba divers, etc. In yet another embodiment a phase modulation spectrophotometer may be employed for calibration of the oximeters described 5 above, especially for in-home or long-term portable monitoring applications, e.g., greater than 3 hours. Such calibration allows more quantitative measure of blood oxygen levels, etc. One example of such a spectrophotometer can be found in U.S. 4,972,331, the 10 entire contents of which is hereby incorporated by reference. It will also be understood that implantable probes may be configured using direct wiring, with corresponding punctures in the skin as an alternative to telemetry.

15 Another preferred embodiment of the present invention is a cognition spectrophotometer system, shown diagrammatically in Figure 15. The cognition spectrophotometer examines the relationship between brain activity, oxygen delivery, oxidative metabolism, and 20 blood flow by employing photon migration from a source placed on the surface of the head through the skin, skull and underlying brain tissues to a detector also located on the surface of the head. As already discussed, light is absorbed and scattered along the migration path.

25 Referring to Figure 15, the system comprises the following five modules: a stimulation module 250, a sensor module 252, a control circuit module 254, an analyzer/display module 256, and a computer/printer module 258. Stimulation module 250 is used to stimulate 30 a specific brain function through a visual, acoustic, sensorimotor, or other stimulation. Sensor module 252 is connected to control circuit module 254; preferred embodiments are shown in Figures 5 through 13, 22, and 23. Figures 10 and 11 diagrammatically show the sensor, 35 control circuit, display and computer/printer modules.

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The display module of Figure 15 is a fast Fourier transform oscilloscope. The operation of sensor module 252 is governed by control circuit module 254 which controls the radiation emission and detection, collects 5 the data, and sends the data to analyzer/display module 256 and to computer/printer module 258. The operation of the whole cognition system is controlled by a computer of computer/printer module 258.

The cognition spectrophotometer system, in one 10 embodiment, measures the low frequency and power spectra of fluctuations of absorbances attributed to the blood concentration changes in the frontal region of the brain. The low frequency recurrences of brain activity are linked to blood concentration increases and are detected 15 in human subjects with an optical device. The spectrophotometer employs wavelengths of light sensitive to oxygenation/deoxygenation of hemoglobin in the red region of the spectrum, i.e., absorbency changes at 760 nm are balanced against those at 850 nm in equal 20 proportions. The difference in the absorbency changes is highly sensitive to the oxygenation/deoxygenation of hemoglobin ( $\text{HbO}_2/\text{Hb}$ ) and is insensitive to the changes of blood concentration. The sum of the absorbency changes 25 of these two wavelengths is sensitive to the blood concentration changes and insensitive to the hemoglobin to oxygenation/deoxygenation of hemoglobin changes (approximately one-half of the 760 nm signal is added to the 850 nm signal). The data reported in Figures 16-21 have been obtained in the sum mode and the time 30 dependence of changes of blood concentration has been measured. An alternative method to the sum of two wavelengths is to use a single wavelength apparatus, shown in Figures 22 and 23, for example, 800 nm which is an isosbestic point in the  $\text{Hb}/\text{HbO}_2$  spectrum. Other 35 wavelengths can be also used, for example, 950 nm which

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is sensitive to water absorption, or wavelengths sensitive to endogenous or exogenous pigments.

The cognition spectrophotometer of Figure 15 was tested on several human subjects who were juniors or 5 seniors from Central and Girls High Schools in West Philadelphia. The subjects were exposed to visual stimulation by a series of abstractions composed of analogies taken from SAT examinations. (All studies were conducted under IRB-approved protocol #M1025 for 10 acquiring optical signals from the forehead of human subjects at rest and under test. Parental approval was obtained for those subjects under 18 years of age.) Sixty of these abstractions were displayed for an intended time of 11 minutes corresponding to 16 15 iterations of the Fourier transform oscilloscope 256 of the display module (Figure 15). The advance of one analogy to the next was dictated by the subject's conclusion that the analogy has been understood. The analogies presented to the subjects in this study were 20 intended to simulate associative responses. The analogies continued within the 11-minute interval as long as the subject felt that he/she was adequately able to concentrate on them. If the subject's attention was diminished due to fatigue, etc., the test was terminated. 25 Usually more than 11 out of the 16 iterations of the Fourier transformations were obtained and often the full 16 were obtained. At this point the subject was told to "rest".

No analogies were presented during the "rest" 30 intervals. The Fourier transformations of the optical data for two successive 11-minute intervals were recorded and subtracted and were entitled "rest"--"rest" (Figure 20).

The sensor module used in this study consisted of 35 two tungsten flashlight bulbs placed 4 cm each from the

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two silicon diodes (4 mm X 10 mm), each equipped with an interference filter transmitting a 10 nm wide band centered at 760 nm and 850 nm. Thus, this system provided two photon migration paths with input-output separation of 4 cm. A preamplifier coupled the optical signals to an amplifier unit that took the sum and difference of the signals suitably corrected as described above. The tungsten lamps were pulsed at 3 Hz so that absorbance measurements were time shared with background measurements and the one was subtracted from the other to provide background light correction via sample and hold techniques for the difference circuit.

In a response speed test, the output of the filtered sum response reached 70% in 1 sec, as shown in Figure 17. The output signal was directly connected to the Fast Fourier transformer Type 440 (Nicolet) which was used in the DC-coupled mode on the 200 millivolts scale. The conditions were set for 16 iterations in the 0-5 Hz scale for a total interval of data acquisition of 10 min. The recording sensitivity was 220  $\mu$ V/cm at x512 gain (Figure 16) and 440  $\mu$ V/cm at x256 gain. The noise level of Figures 16-20 was about 20 mV. The total signal was 115 mV and the noise level was 0.2%. The full scale sensitivity was 1.0% of absorbance change at x512 and 2.0% at x256. Figure 16 illustrates the response of the Fourier transform oscilloscope to 300  $\mu$ V peak-to-peak square wave (top trace) and 225  $\mu$ V sine wave (lower trace), wherein 16 iterations at x512 gain were used.

Referring to Figure 17, the response of the DC amplifier to a square wave reaches 70% in 1 sec. Thus, the system is responsive only to frequency components in the 0-3 Hz region and records the recurrence of these components. Static experiments carried out simultaneously indicate that the sum of the peaks of the

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test trace corresponds to an increase of blood concentration of approximately 5% of the total signal.

The ideal study control would repeat every feature of the study except the specific changes due to 5 recognition of the analogies given to the subjects. Thus, the study was repeated with two intervals of "rest" of duration equal to that of the "rest"--"test" study. The "test"--"test" was not considered appropriate because the double duration of the "test" might have led to 10 accommodation in the responses, and because the response to different "tests" could be different. This study had the sensor module placed in one location during the test interval; however, mapping of the "test" response by locating the sensor module in different locations on the 15 exterior of the head is feasible.

Each recurrent signal is indicated by a peak at a particular frequency (Hz) in the illustrations. Peaks present in the "rest" recording are usually related to arterial pulse and related frequencies. Additional 20 frequencies are usually observed in the "test" interval, and the Fournier transforms are readily subtracted by the instrument ("test"--"rest"). Some recurrent frequencies may also contribute to the increasing intensity of the spectra in the low frequency region. Peak size, as well 25 as the  $1/f$  noise is increasing as the frequency decreases.

Both the "test" and "rest" signals contain a signal of the arterial pulse of the brain tissue. At "rest" and "test", signals at 1-2 Hz and related 30 harmonics are often observed. At "rest", a low frequency component is detected at various locations on the forehead and tracks closely the frequency of arterial pulse as detected on the wrist. However, these signals nearly completely cancel in the "rest"--"rest" difference 35 Fourier and are thus attributed to the arterial pulse in

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the brain tissue. Occasionally, the "test"--"rest" shows a difference signal due to altered arterial pulse rate during the "test".

Referring to Figures 18 and 19, the Fourier transform spectrum of the "test" interval and the "rest" interval of a female subject (U) are displayed as traces b and a, respectively. 16 out of the 16 scans were obtained (study 24, Table I). The frequency scale is 0-5 Hz, the amplitude scale represents a gain of x256. The subject's heart rate was 81 BPM (1.3 Hz). However, in the "rest" spectrum, the predominant peak is at 0.8 Hz, approximately 2% of the total signal. Small, sharp peaks appear at 1.7, 2.7, 3.5 and 4.7 Hz. Similar peaks of similar amplitude appear in the "test" study and are thus not "activity related". However, new large peaks appear at 1.6 and 1.8 Hz in the test spectrum.

The difference of the two Fourier transforms designated "test"--"rest" shows a recurrence of signals at particular frequencies associated with presentation of analogies. There is a preponderance of the 0.8, 1.6 and 1.8 Hz peaks and a small contribution of a 2.8 Hz peak. The largest peak corresponds to 1% of the total signal. Of interest from the theoretical standpoint is a large component of  $1/f$  noise in the "test"--"rest" diagram suggesting that recurrence at the very low frequencies is less probable than at the higher frequencies. In a repetition of this study (#25), a 2.3 Hz peak was observed (see Table I) and the doublet peaks at 1.7 and 1.9 Hz were again observed in "test"--"rest".

Another frequency spectrum of a female subject (B) is shown in Figure 19 where the rest spectrum shows a strong peak at 0.8 Hz, presumably due to the heart rate, and a second peak at 2.7 Hz. After 7 iterations, the subject spontaneously ceased the study. The Fourier transform of the "test"--"rest" spectrum contains broad

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peaks at 0.8, 1.5, 2.0, 2.7 and a peak at 4.3 Hz. The largest peaks exceed 1% of the total signal. The 1/F noise observed in the spectra appears to contain an unresolved peak at 0.2 Hz.

5 Referring to Figure 20, frequency analysis of two "rest" spectra of a subject U shows somewhat stronger peaks than in the "rest" study of Figure 18 at 1.2 and 2.3 Hz with a small peak at 4.6 Hz. In the "rest"- "rest" traces, only small broad peaks are observed. There are 10 small differences that are attributed to variations in the arterial pulse and its higher frequency components of amplitude and frequency that differ in the first "test" as compared to the second. This is confirmed in Tests 27 and 28. In no case was a new distinctive peak observed 15 as in "test"- "rest" studies. Table I summarizes 31 tests of 9 individuals (6 females, 3 males) over a six-week period. Column F lists the frequencies observed at "rest", Column G, the frequencies during the "test" interval (except Cases 8, 27, 28). Column H gives the 20 recurrence of frequencies appearing in the subtraction of "test" and "rest" in the Fourier transform. A high consistency is indicated by our observation of recurring frequencies in 24 out of 28 tests (85%) (all but four tests 2, 3, 9, and 24). In No. 24, increased 1/f noise was 25 observed (Column H). Tests 8, 27, 28 were controls in which "rest"- "rest" intervals were subtracted.

Referring to Figure 21, the histogram displays the recurrence of frequencies in the range 0-4 Hz taken from Column H of Table I. Each individual's frequencies are 30 cross hatched. There appears to be a preponderance of 1-2 Hz signals taking into account that the frequency range is limited by commingling with 1/f noise at the low end, and the frequency response of the instrument diminishes signals above 2.5 Hz.

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The intensity value at the particular frequency gives the power spectrum of Figure 21a for 1 Hz intervals. The largest peak is at 1.5-2.5 Hz. In both cases, the stippling of the chart identifies the nine 5 subjects.

A more detailed plot of the data of Table I, including those that exhibited three or more frequencies, indicated that this ensemble exhibited equal maxima at the harmonic frequencies 0.8 and 1.6 Hz and approximately 10 equal peaks at 1.2, 2.6 and 4.2 Hz respectively, a rough approximation to harmonics of frequencies of 0.08 and 1.2 Hz. However, there was no peak at 3.0, 2.1 Hz at the exact harmonic frequencies.

The cognition spectrophotometer system, used in 15 this trial, utilizes only the sum of the 760 nm and 850 nm signals. The isosbestic point in the Hb/HbO<sub>2</sub> spectrum is approximately at 800 nm, and thus the balanced sum of Hb/HbO<sub>2</sub> absorbances at 760 and 850 nm measures the blood concentration. Hb/HbO<sub>2</sub> is the principal absorber at 20 these wavelengths since the signal is over 20 times that of cytochrome aa<sub>3</sub>. The fact that no significant results were obtained in the difference recording suggests that the oxygenation/deoxygenation of the frontal lobe tissue was not a predominant effect in these studies. Changes 25 of light scattering are not separated from absorbance changes when using continuous light, and would be expected to uniformly affect both 760 and 850 nm.

Furthermore, results of the present trial are compatible with other studies using PET, SPEC, and MRI 30 which also suggest existence of blood flow changes during brain stimulation and the fact that the arterial pulse is the strongest signal in both "rest" and "test"; this supports the interpretation attributing the measured signal to blood concentration changes.

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It is expected that the metabolic activities induced by brain stimulation contain low frequency component signals. The cognition spectrophotometer system of Figure 15 records repetitive fluctuations in 5 the optical signal in a 10 min stimulus interval. Thus, the employed method requires not only a blood concentration increase during stimulation, but also periodic repetition of the increase within the tissue volume optically sampled. Such increases need not be 10 repeated at identical locations but may have a spatio-temporal distribution. A 4 cm separation of input/output gives a mean penetration of 2 cm and a tissue volume of roughly 5 ml within which the repetitive response is observed.

15 Our narrow band width and relatively short iteration time (<11 min.) in this trial was set by the characteristics of an available instrument, and the detected spectrum may be only a portion of the total frequency spectrum. As shown in Figure 22, a much faster 20 instrument can be also used. The limits to the bandwidth of optical studies are set both by signal-to-noise and by the intrinsic relaxation time of photon migration in the brain.

In the above described trial only a crude 25 localization of the response was employed by placement of the input and output ports. The optical system was designed to respond optimally to blood concentration changes (in a volume of about 3-5 ml) in the frontal/temporal cortex, and the analogies were designed 30 to stimulate activity in the frontal region. When left and right sides of the forehead were compared, the success rate of new peaks in the Fourier transform was two times greater in the left side.

An important aspect of future development of the 35 optical methods is the rate at which data may be

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accumulated. The travel time of photon migration over a path length of one meter is 23 ns with a 4 cm input/output separation. The signal to noise ratio will determine the number of iterations of the test, which in 5 these preliminary studies, was approximately 50 over a period of 11 minutes.

The photon migration kinetics are responsive to both light scattering and light absorption. Whilst absorption has been stressed in these studies, light 10 scattering is much closer to the primary events of neuronal/axonal response than to the blood flow/blood concentration change, both in anatomy and in time.

In this trial, the low frequency recurrence of changes of blood concentration was measured in portions 15 of the brain that are approximately 2 cm deep from the surface of the skull of the subjects. Application to other stimuli (for example, visual, acoustic, sensorimotor) that affect function in other regions of the brain may be possible. (Visual stimulation 20 registered in the visual cortex was not used in the present trial because dense hair covered the surface of the back of the head in the population studied.) It is expected that the recurrence frequencies which are observed in the cognitive tests would be significantly 25 diminished in cases of neuronal deterioration. Thus, the cognition spectrophotometer system enables simple non-invasive and rapid testing of cognitive function of different regions of the brain.

The cognition spectrophotometer system is designed 30 to provide objective evaluation of functional activity of the brain with a simple and inexpensive device. The system enables a wide range of studies of the brain activity in responding to appropriate tasks and presents an alternative to several expensive techniques (for 35 example, MEG and EEG) or ones that involve radioactive

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techniques. Thus, screening for neuronal deterioration and/or deterioration of brain function can be done conveniently and continuously.

In another embodiment, shown in Figures 22 and 23, 5 the cognition spectrophotometer simultaneously records lateralized potential difference of two brain hemispheres. It has been suggested that lateralized readiness potential can measure electrical brain activity that is related to preparation of movement. This measure 10 has been used to illuminate pre-setting processes that prepare the motor system of the brain for action. The lateralized potential also demonstrates the presence of transmission of partial information in the cognitive system and identifies processes responsible for the 15 inhibition of responses.

The cognition spectrophotometer, shown in Figures 22 and 23, measures the lateralized difference potential optically by measuring increased blood concentration in localized regions of the brain that are activated by the 20 lateralized readiness potential. The spectrophotometer simultaneously records and compares optical signals from both hemispheres. The detected data are subtracted in real time, the difference signal is recorded as an analog signal via an A/D converter and a computer manipulates 25 the data and takes the Fourier transform of the data. The lateralized difference potential is measured as blood concentration changes using 800 nm light; however, light of other wavelengths sensitive to other constituents of the brain tissue can be used.

30 For high frequency measurements, the cognition spectrophotometer can use a fast lateralization detector, shown in Figure 22. The detector has two tungsten light sources 200 placed on the left and right parietal bones and two light-to-frequency converters 202 placed also on 35 the parietal bones at a distance of 4 centimeters from

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the sources. The intensity of each lamp 200 is regulated differentially by a lamp balance 206 in order to achieve the same light intensity output from the two light sources. An 800 nm interference filter 208 is placed on 5 each silicon detector 202. The silicon light-to-frequency converters are adjusted by the frequency light intensity control to output the same frequency in the range of  $10^6$  to  $10^7$  Hz.

The fast lateralization detector measures a 10 frequency difference between the two silicon detector converters 204. The signal of each detector is routed to a differential counter 212 using a 50 Hz clock 210. If the differential count is zero, both detectors are outputting the same frequency signal. If there is a 15 difference in the signals detected at the two detectors, the differential count is not zero. The differential signal is processed by a frequency-to-voltage converter 214. Converter 214 operates in a low frequency range and detects frequency differences. The voltage output is 20 Fourier transformed, stored and analyzed in view of a visual stimulus 218 or other brain activity stimulus.

Referring to Figure 23, in another preferred embodiment the cognition spectrophotometer utilizes a narrow band lateralization detector which is sensitive to 25 the low frequency changes. Tungsten lamps 228 placed on the parietal bone are flashed at frequencies on the order of 2 to 3 Hz in order to provide for correction of the dark current. Each detector 230 has an 800 nm interference filter 232. A differential amplifier 234 is 30 used to measure difference in the light intensity arriving at the two detectors. The output of the differential amplifier is coupled to the "RunMan" control unit, a modified version of the control unit shown in Figures 10 and 11. Balance 240 is set so that the two 35 signals are balanced at zero millivolts. The output

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signal is connected to the fast Fourier transformer 242, recorded on the strip chart recorder 244 or send to a computer. The lateralization detector of Figure 23 measures differential low frequency fluctuations of 5 absorbances attributed to the brain blood concentration changes in different respective regions of the two brain hemispheres. The localization of the radiation to the appropriate region of the brain hemisphere is achieved by selecting proper location and separation of the input and 10 output ports of the source-detector pair (Figures 15, 22, 23 and 24). For example, as described above, 4 cm separation of the source and detector on the exterior of the head gives a penetration of about 2 cm of the banana-shaped migration path of the radiation.

15 Referring to Figure 24, another preferred embodiment of the present invention is a differential spectrophotometer system for in vivo examination of a tissue of a human by measuring changes in electromagnetic radiation migrated in a path of two localized tissues of 20 interest. The first tissue of interest, used to collect reference data, is expected to have normal physiological properties. The second tissue of interest is a tissue expected to have regions of pathological or pathophysiological changes, for example, a tumor or 25 bleeding. An approximate localization of the tissue of interest having pathological or pathophysiological changes can be determined by diagnostic assessment of the subject, for example, by a neurologic examination, evaluation of the symptoms, etc.. In absence of any 30 pathophysiological changes both the first and second localized tissues of interest (for example, regions of the left and right hemisphere of the brain, left and right breast, or left and right arm) are expected to produce nearly identical signals of photon migration. On 35 the other hand, if a region of an organ, for example, the

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right hemisphere of the brain, has a tissue of abnormal pathophysiological state, the tissue is expected to produce a signal which differs from the signal of the normal tissue of the left hemisphere; thus, the 5 differential signal will be non zero.

Referring to Figure 24, the differential spectrophotometer system comprises the following five modules: two sensor modules 271 and 272, a control circuit module 274, an analyzer/display module 276, and a 10 computer/printer module 278. Each of the two sensor modules 271 and 272, placed on the subject's head 273, comprises at least one source and detector as shown in Figures 5 to 8c, 22, 23. The operation of each sensor module is governed by control circuit module 274 which 15 controls the radiation emission and detection, collects the data and sends the data to analyzer/display module 276 and to computer/printer 278. The operation of the whole cognition system is controlled by a computer of computer/printer module 278.

20 The differential spectrophotometer introduces electromagnetic radiation of at least one selected wavelength (for example, 800 nm) into the brain simultaneously at a first and second input port of the 271 and 272 sensor modules. Both the first input port 25 and the second input port are placed at a first selected location and a second selected location on the exterior of the head, respectively. Two detectors, placed at a first and second location on the exterior of the head, are simultaneously detecting radiation that migrated 30 along the banana-shaped paths in the two brain hemispheres from the first and second input ports to the first and second output ports, respectively. Control module 274 collects the detector signals, corrects for the noise signals and sends the corrected signals to 35 analyzer/display module 276 and to computer/printer

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module 278. Control module 274 can also create a differential signal, as described in Figures 22 and 23.

The system processes the signals of the two detectors and evaluates the processed data to determine 5 whether the radiation migrated in a tissue of abnormal physiological or pathophysiological properties.

In another application, the differential spectrophotometer system can be used to determine physiological or pathophysiological properties of a 10 breast tissue. Here, one sensor is placed on one breast and the other sensor on the other breast. Similarly as for the brain, breast tissue is examined by comparing the two signals of the radiation that migrated in the two paths in the respective breast.

15 The lateralized detection technique that simultaneously measures photon migration in two migration paths (Figures 22, 23, and 24) achieves better signal-to-noise ratio than the technique which detects signals from only one migration path (Figure 15). Some 20 lateralized events involve only blood volume changes or only blood concentration changes; thus, the system can probe the tissue using radiation of only one selected wavelength. Other lateralized events may result in oxygenation/deoxygenation changes; thus, the system uses 25 radiation of at least two wavelength (for example, 760 nm and 850 nm) coupled into an organ alternatively. In this case, each sensor comprises either one source-detector pair adapted to operate at at least two selected wavelengths, or two wavelength specific source-detector 30 pairs. Signals of each wavelength obtained from the two sensors are again differentially manipulated to determine desired tissue properties. As described above, the localization of the radiation is controlled by placement and position of each source and detector.

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One of ordinary skill in the art will appreciate that the present invention is not limited to the particular embodiments described in detail. Modifications to the circuitry disclosed, and other 5 aspects of the spectrophotometer configurations disclosed, as well as other modifications to the physical arrangement of the present apparatus will be obvious to those of ordinary skill. Further, the present invention is not limited to any of the uses described herein. In 10 order to fully appreciate the scope of the present invention, reference should be made to the following claims.

What is claimed is:

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Claims

1. An oximeter for determining the oxygenation state of localized body tissue per se, constructed to be worn over a period of activity by a user and comprising a 5 flexible, body-conformable support member which supports, adjacent the skin of a user, over the localized tissue of interest, at least a pair of spaced apart light sources, and intermediate thereof, at least a pair of wavelength-specific photo detectors, each light source exposed to 10 transmit wavelengths of both of said specific wavelengths toward the localized tissue of interest lying below the skin and below the associated subcutaneous fat layer of the user, and each detector exposed to receive photons of the respective specific wavelength that have originated 15 from each light source, and scattered from the localized tissue and passed back to the detectors through the subcutaneous fat layer and skin of the user, the support member including conformable barrier means disposed between each light source and the detectors, said barrier 20 means being of substance capable of conforming to the contour of the wearer and preventing light energy proceeding laterally in the region of the barrier means from reaching the detectors.

2. An oximeter for determining the oxygenation 25 state of localized body tissue per se, constructed to be worn over a period of activity by a user and comprising a flexible support member which supports, over the localized tissue of interest, at least a pair of spaced apart light sources, and intermediate thereof, at least a 30 pair of wavelength-specific light detectors, each light source exposed to transmit wavelengths of both of said specific wavelengths toward the localized tissue of interest, and each detector exposed to receive photons of

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the respective specific wavelength that have originated from each light source, and scattered from the localized tissue and passed back to the detectors.

3. The oximeter of claim 1 or 2 in which the 5 light sources comprise broad spectrum CW light sources.

4. The oximeter of claim 3 in which the light sources comprise tungsten filament lamps.

5. The oximeter of claim 1 or 2 including control means for simultaneously flashing the light sources to 10 enable each detector to pick up light energy at its specific wavelength simultaneously from each light source.

6. The oximeter of claim 1 or 2 including means constructed to flash said light sources at selected 15 intervals unrelated to the interval of heart beats of the user.

7. An oximeter comprising a flexible support member comprised of a molded-elastomeric backing member, said backing member mounting at least one light source 20 means capable of producing two selected wavelengths and oriented to direct said light to tissue of a user and said backing member mounting detector means capable of separately detecting energy at each of said wavelengths scattered by tissue of the user, integral elastomeric 25 portions of said backing member defining a barrier exposed for conformable contact with an exposed surface of the user, in position to prevent lateral movement of light in subcutaneous layers from the source means to the detector means.

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8. An oximeter comprising a flexible support member, said support member mounting at least one light source means capable of producing two selected wavelengths and oriented to direct said light to tissue 5 of a user and said support member mounting detector means capable of separately detecting energy at each of said wavelengths scattered by tissue of the user, said support member supporting a barrier member exposed for conformable contact with an exposed surface of the user 10 in position to prevent lateral movement of light from the source means to the detector means, said barrier comprising a member having an edge sized and positioned to indent skin and the flesh of the user thereby to intercept light migrating laterally in the subcutaneous 15 fat layer and prevent such light from reaching said detector means.

9. The oximeter of claim 8 wherein said barrier member is elastomeric, adapted to conform to the contour of the skin of the wearer.

20 10. The oximeter of claim 9 wherein said flexible support member comprises a molded-elastomeric backing member and said barrier member is integral with said backing member.

11. The oximeter of claim 8, 9 or 10 wherein the 25 member defining said flesh-indenting edge is about 0.5 cm thick in the region that engages the skin.

12. The oximeter of claim 7 or 8 wherein said barrier member comprises a rib-form member.

13. The oximeter of claim 7 or 8 including in 30 series at least two barrier members, one closely adjacent

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to said light source means and one closely adjacent to said detector means.

14. The oximeter of claim 7 or 8 in which said support member mounts two spaced-apart light sources and 5 a pair of detectors are disposed parallel to each other, disposed laterally relative to the line between said light sources and equal distance from each of said light sources.

15. The device of claim 14 wherein said light 10 sources comprise broad spectrum CW light sources.

16. The oximeter of claim 1, 2, 7 or 8 including electronic control circuitry for said light source and said detector means, the circuitry disposed upon a miniature semiconductor chip carried by said support 15 member.

17. The oximeter of claim 1, 2, 7 or 8 in combination with a real-time readout device constructed to be worn by the user and having a display responsive to said oximeter disposed for viewing by the user.

20 18. The oximeter of claim 17 wherein said oximeter is associated with means securing it to an appendage of the user and said readout device is constructed to be worn by a user.

25 19. The oximeter of claim 1, 2, 7 or 8 in combination with radio frequency telemetry means for transmitting oximeter data on a real time basis to a station remote from the user or to a receiver in a readout device constructed to be worn by a user.

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20. The oximeter of claim 1, 2, 7 or 8 including electronic control circuitry for said light source and said detector means, the circuitry disposed upon a miniature semiconductor chip carried by said support member in combination with radio frequency telemetry means controlled by said circuitry for transmitting oximeter data on a real time basis to a station remote from the user.

21. The oximeter of claim 1, 2, 7 or 8 including means for battery-operation of said oximeter and means to record oximetry data in internal digital memory for subsequent display or data analysis on a computer.

22. The oximeter of claim 1, 2, 7 or 8 including electronic control circuitry for said light source and said detector means, the circuitry disposed upon a miniature semiconductor chip carried by said support member, and means for battery-operation of said oximeter and means to record oximetry data in internal digital memory for subsequent display or data analysis on a computer.

23. The oximeter of claim 7 or 8 encapsulated in biocompatible material, the oximeter constructed and arranged for implantation under the skin of a user for monitoring internal tissue oxygen trends.

24. An oximeter comprising a support mounting a light source and detector means at fixed spacing, and electronic control circuitry for said light source and said detector means, the circuitry disposed upon a miniature semiconductor chip carried by said support member, said oximeter encapsulated in biocompatible water impermeable material, the oximeter constructed and

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arranged for implantation under the skin of a user for monitoring internal tissue oxygen trends.

25. The method of monitoring the derivative or rate of change of the time based curve representing 5 detected change of tissue oxygen levels and blood volume and employing these rates as a quantitative standard of measurement of tissue oximetry.

26. The method of assisting an aviator or other person engaged in activity that can subject the person to 10 high G-forces including providing to the person a comfortable oximeter sensor suitable to be worn about the head and capable of responding to tissue oxygen level, blood volume of brain tissue on a real time basis, employing said oximeter sensor to monitor oxygen level of 15 brain tissue of the wearer as the wearer engages in said activity, comparing the monitored value to a standard and generating a signal, such as a warning or control signal, in the event the monitored level violates a pre-established standard.

20 27. The method of claim 26 wherein said oximeter is constructed to monitor the trend of oxygen level in the brain, and means to evaluate the rate of change being detected and using said rate of change as the control value and alarm reference.

25 28. The method of monitoring a person suspect of sleep apnea or sudden infant death syndrome including providing to the person a comfortable oximeter sensor capable of automatically responding to oxygen level of the person while permitting the person to sleep, 30 automatically monitoring the output of the oximeter by comparing it to a standard and generating a signal, such

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as a warning or control signal, in the event the monitored level violates a pre-established standard.

29. The method of claim 28 wherein the oximeter sensor is taped comfortably to the head for monitoring.

5. 30. The method of claim 28 used in conjunction with impedance pneumography (breathing rate measurement using chest-wall impedance) and/or EKG to provide an effective in-home apnea monitor to alarm the patient or other individuals in the area so as to wake the patient 10 and prevent hypoxic tissue damage during sleep.

31. The method of monitoring the cerebral tissue oxygen rate of change as a means of triggering alarm to awaken a subject in danger of infarct due to hypoxia.

15 32. The method of monitoring both tissue oxygen level and blood volume in skin flaps such as are produced either by wound or surgery, as said flaps heal, the separation between the source and the detector being established in relation to the thickness of the skin flap to ensure tissue of the flap per se is being monitored.

20 33. The method of emergency monitoring of cerebral tissue oxygen level and blood volume in an emergency care situation with the device of claim 21.

25 34. The method of employing the device of any of the claims 1, 2, 7, or 8 wherein the oxygen levels, blood volume, and/or rate of change are measured in cancerous tissue to indicate the activity and viability of the tissue.

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35. The method of employing the device of claim  
24 wherein the oxygen levels and blood volume are  
measured in cancerous tissue to indicate the activity and  
viability of the tissue.

5 36. The method of claim 34 including monitoring  
of the viability of a tumor following treatment intended  
to wipe out said cancerous tissue.

37. A helmet into which is molded a tissue  
oximeter in position to engage the head of the wearer  
10 when the helmet is put on, the oximeter being of the NIR  
type, comprising light source means for transmitting near  
infrared light into the head, detector means held in  
spaced position relative to the light source means for  
receiving light scattered by brain tissue and a barrier  
15 disposed to engage the head between the light source  
means and the detector means to prevent light traveling  
laterally from the light source means from reaching the  
detector means.

38. The helmet of claim 37 wherein the oximeter  
20 includes control circuitry on a miniature chip.

39. The helmet of claim 37 or 38 including means  
for determining the rate of change of oximetry readings  
and for comparing the rate of change to a standard.

40. A tissue oximeter comprising a support, a  
25 detector fixed to the support and a light source mounted  
in an adjustable manner to the support to enable  
selection of the spacing between light source and  
detector for adjusting the mean depth of tissue to which  
the oximeter responds.

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41. A tissue oximeter in combination with means connected to receive tissue oxygen readings from the oximeter, determine the rate of change of said readings, said rate of change serving as a quantifiable indication 5 of the state of the metabolic process of the tissue.

42. The oximeter of claim 1, 2, 7 or 8 including electronic control circuitry comprised of entirely non-magnetic components enabling use of the device in conjunction with nuclear magnetic resonance imaging.

10 43. An oximeter disposed on an endoscope, catheter, guidewire or the like for insertion via a body passage to internal tissue, and including means such as an inflatable balloon to press the oximeter sensor against the localized tissue of interest.

15 44. The oximeter of claim 1, 2, 7, or 8 including a water impermeable coating about said device for applications in the presence of water.

45. The oximeter of claim 1, 2, 7, or 8 wherein said light source comprises a light emitting diode.

20 46. The oximeter of claim 1, 2, 7, or 8 wherein said detector comprises a silicon diode.

47. The oximeter of claim 1 or 2 wherein said wavelength specific detector comprises a silicon diode and an interference filter.

25 48. The oximeter of claim 1, 2, 7, or 8 including electronic control circuitry for said light source and said detector, said circuitry being adapted to correct

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for a noise signal not attributable to detected light that migrated through said localized tissue of interest.

49. The oximeter of claim 48 wherein said correction of said noise signal being achieved by  
5 charging a capacitor of an integrator for said detector with current of one polarity during a light off cycle and subsequently charging said capacitor with current of opposite polarity during a light on cycle, whereby subtracting said noise signal occurring during said light  
10 off cycle from the total signal occurring during said light on cycle.

50. A method of transcranial examination of brain activity by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in  
15 the brain comprising

(a) introducing electromagnetic radiation of a selected wavelength into the brain at an input port placed at a selected location on the exterior of the head,  
20 (b) detecting, at a detection port placed at a selected location on the exterior of the head, radiation of said selected wavelength that has migrated in the brain,

(c) causing stimulation of a brain activity while  
25 introducing said radiation at said input port and while detecting radiation of said detection port,

(d) processing signals of said detected radiation that has migrated in the brain to create processed data, and

30 (e) determining a characteristic of said brain activity by correlating said processed data with said caused stimulation of said brain activity.

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51. The method of claim 50 wherein said steps of introducing said radiation into the brain and detecting said radiation that has migrated in the brain, while causing stimulation of said brain activity, are repeated 5 at different locations on the exterior of the head, and said step of processing said detected radiation to create processed data is correspondingly repeated.

52. The method of claim 50 or 51 wherein said input port and said output port are located on one of the 10 following: the frontal bone, parietal bone, temporal bone or occipital bone; said input port and said output port being separated by a predetermined distance in order to localize said migration of said radiation to a selected region of the brain.

15 53. The method of claim 52 wherein said predetermined distance is 4 centimeters.

54. The method of claim 50 further comprising (a) introducing electromagnetic radiation of said selected wavelength into the brain at a second input port 20 placed at a second selected location on the exterior of the head,

(b) detecting, at a second detection port placed at a selected location on the exterior of the head, radiation of said selected wavelength that has migrated 25 in the brain from said second input port to said second detection port,

(c) processing signals of said detected radiation that has migrated in the brain from said second input port to said second detection port to create second 30 processed data, and

(d) determining a characteristic of said brain activity by correlating both first mentioned and said

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second processed data with said caused stimulation of said brain activity.

55. The method of claim 54 wherein said radiation is simultaneously introduced at said first and second  
5 input ports and detected at said first and second detection ports.

56. The method of claim 54 wherein said radiation is first introduced at said first input port and detected at said first detection port, and subsequently said  
10 radiation is introduced at said second input port and detected at said second detection port.

57. A method of transcranial examination of brain activity by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in  
15 the brain comprising

(a) introducing electromagnetic radiation of a selected wavelength into the brain simultaneously at a first input port and at a second input port, said first input port and said second input port being placed at a  
20 first selected location and a second selected location on the exterior of the head, respectively,

(b) detecting simultaneously, at a first detection port placed at a selected location on the exterior of the head, radiation that has migrated in the  
25 brain from said first input port to said first detection port and, at a second detection port placed at second selected location on the exterior of the head, radiation that has migrated in the brain from said second input port to said second detection port,

30 (c) causing stimulation of a brain activity while introducing said radiation at said first and second input

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ports and while detecting radiation at said first and second detection ports,

(d) processing signals of said detected radiation that has migrated in the brain to create processed data,

5 and

(e) determining a characteristic of said brain activity by correlating said processed data to said caused stimulation of said brain activity.

58. The method of claim 54 or 57 wherein said 10 first input port and said first output port are located on one parietal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the respective hemisphere of the brain, and said second input port and 15 said second output port are located on the other parietal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the other hemisphere of the brain.

59. The method of claim 58 wherein said 20 processing comprises comparing electromagnetic radiation detected at said first and second detection ports to create processed data representing a differential signal.

60. The method of claim 54 or 57 wherein said first input port and said first output port are located 25 on one temporal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the respective hemisphere of the brain, and said second input port and said second output port are located on the other temporal 30 bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the other hemisphere of the brain.

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61. The method of claim 60 wherein said processing comprises comparing electromagnetic radiation detected at said first and second detection ports to create processed data representing a differential signal.

5. 62. The method of claim 50, 54 or 57 wherein said processing of said detected radiation comprises Fourier transformation.

63. The method of claim 50, 54 or 57 wherein said stimulation is visual stimulation.

10 64. The method of claim 50, 54 or 57 wherein said stimulation is acoustic stimulation.

65. The method of claim 50, 54 or 57 wherein said stimulation is sensorimotor stimulation.

15 66. The method of claim 50, 54 or 57 further comprising examining cognitive function of a selected region of the brain based on correlation between said processed data and said caused stimulation of said brain activity.

20 67. The method of claim 50, 54 or 57 further comprising examining pathological/pathophysiological state of a tissue of a selected region of the brain based on correlation between said processed data and said caused stimulation of said brain activity.

25 68. A cognition spectrophotometer system for transcranial examination of brain activity by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in the brain comprising

- 70 -

(a) a light source adapted to introduce electromagnetic radiation of a selected wavelength into the brain at an input port placed at a selected location on the exterior of the head,

5 (b) a detector adapted to detect, at a detection port placed at a selected location on the exterior of the head, radiation of said selected wavelength that has migrated in the brain,

(c) stimulation means adapted to cause 10 stimulation of a brain activity while introducing said selected wavelength and while detecting radiation at said detection port,

(d) processing means adapted to process signals of said detected radiation that has migrated in the brain 15 to create processed data, and

(e) evaluation means adapted to determine a characteristic of said brain activity by correlating said processed data with said caused stimulation of said brain activity.

20 69. The system of claim 68 wherein said processing means adapted to process detected radiation that has migrated in the brain in said migration path between said input port and said output port being separated by a predetermined distance and being located 25 at different locations on the exterior of the head.

70. The system of claim 68 or 69 wherein said input port and said output port are located on one of the following: the frontal bone, parietal bone, temporal bone or occipital bone; said input port and said output port 30 being separated by a predetermined distance in order to localize said migration of said radiation to a selected region of the brain.

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71. The system of claim 70 wherein said predetermined distance is 4 centimeters.

72. The system of claim 68 further comprising

(a) a second light source adapted to introduce 5 electromagnetic radiation of said selected wavelength into the brain at a second input port placed at a second selected location on the exterior of the head,

10 (b) a second detector adapted to detect, at a second detection port placed at a selected location on the exterior of the head, radiation of said selected wavelength that has migrated along said migration path in the brain from said second input port to said second detection port, and

15 (c) processing means adapted to process signals of said detected radiation that has migrated in the brain from said second input port to said second detection port to create second processed data,

20 wherein said evaluation means determine said characteristic of said brain activity by correlating both first mentioned and said second processed data with said caused stimulation of the brain.

25 73. The system of claim 72 adapted to introduce simultaneously said radiation at said first and second input ports and detect at said first and second detection ports.

74. The system of claim 72 adapted to introduce said radiation first at said first input port and detected at said first detection port, and subsequently introduce said radiation at said second input port and 30 detected at said second detection port.

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75. A cognition spectrophotometer system for transcranial examination of brain activity by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in the brain comprising

5 (a) a first light source and a second light source adapted to introduce electromagnetic radiation of a selected wavelength into the brain simultaneously at a first input port and at a second input port, said first input port and said second input port being placed at a 10 first selected location and a second selected location on the exterior of the head, respectively,

15 (b) a first detector and a second detector adapted to detect simultaneously, at a first detection port placed at a selected location on the exterior of the head, radiation that has migrated in the brain from said first input port to said first detection port and, at a second detection port placed at second selected location on the exterior of the head, radiation that has migrated 20 in the brain from said second input port to said second detection port,

25 (c) stimulation means adapted to cause stimulation of a brain activity while introducing said radiation at said first and second input ports and while detecting radiation at said first and second detection ports,

(d) processing means adapted to process signals of said detected radiation that has migrated in the brain to create processed data, and

30 (e) evaluation means adapted to determine a characteristic of said brain activity by correlating said processed data to said caused stimulation of said brain activity.

76. The system of claim 72 or 75 wherein said first input port and said first output port being located

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on one parietal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the respective hemisphere of the brain, and said second input port and 5 said second output port being located on the other parietal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the other hemisphere of the brain.

77. The system of claim 76 wherein said 10 processing means further adapted to compare electromagnetic radiation detected at said first and second detection ports to create processed data representing a differential signal.

78. The system of claim 72 or 75 wherein said 15 first input port and said first output port are located on one temporal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the respective hemisphere of the brain, and said second input port and 20 said second output port are located on the other temporal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the other hemisphere of the brain.

79. The system of claim 78 wherein said 25 processing means further adapted to compare electromagnetic radiation detected at said first and second detection ports to create processed data representing a differential signal.

80. The system of claim 68, 72 or 75 wherein said 30 processing of said detected radiation comprises Fourier transformation.

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81. The system of claim 68, 72 or 75 wherein said stimulation means adapted to cause visual stimulation.

82. The system of claim 68, 72 or 75 wherein said stimulation means adapted to cause acoustic stimulation.

5 83. The system of claim 68, 72 or 75 wherein said stimulation means adapted to cause sensorimotor stimulation.

10 84. The system of claim 68, 72 or 75 wherein said evaluation means further adapted to examine cognitive function of a selected region of the brain based on correlation between said processed data and said caused stimulation of said brain activity.

15 85. The system of claim 68, 72 or 75 wherein said evaluation means further adapted to examine tissue of a selected region of the brain based on correlation between said processed data and said caused stimulation of said brain activity.

20 86. The system of claim 75 wherein said first light source and said second light source are tungsten lamps or light emitting diodes.

87. The system of claim 75 wherein said first detector and said second detector are silicon diodes each having an interference filter adapted to detect said radiation of said selected wavelength.

25 88. The system of claim 75 wherein said first detector and said second detector are light-to-frequency

- 75 -

convertors each having an interference filter adapted to detect said radiation of said selected wavelength.

89. The system of claim 88 wherein said processing means comprise

5 (a) differential counter adapted to register differential signals received from said light-to-frequency convertors,

(b) clocking means adapted to route signals of said detected radiation from said light-to-frequency

10 convertors to said differential counter, and

(c) a frequency-to-voltage converter adapted to convert signals from said differential counter.

90. The system of claim 89 wherein said processing means further comprise a fast Fourier

15 transformer adapted to process differential signal from said frequency-to-voltage converter.

91. The system of claim 90 wherein said evaluation means comprise a storage oscilloscope adapted to analyze the Fourier transformed differential signal of 20 said fast Fourier transformer.

92. The system of claim 89 or 91 wherein said evaluation means further comprises computational means adapted to analyze said differential signal.

93. A cognition spectrophotometer system for 25 transcranial examination of brain activity by measuring changes in light scattered and absorbed in a migration path in the brain comprising

(a) the oximeter of claim 2 or 7,

(b) stimulation means adapted to cause

30 stimulation of a brain activity while introducing said

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light using said light source and while detecting said light that migrated in the localized tissue of interest of the brain,

5 (d) processing means adapted to process signals of said detected light that has migrated in the brain to create processed data, and

10 (e) evaluation means adapted to determine a characteristic of said brain activity by correlating said processed data to said caused stimulation of said brain activity.

94. A method of transcranial examination of a brain tissue by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in the brain comprising

15 (a) introducing electromagnetic radiation of a selected wavelength into the brain simultaneously at a first input port and at a second input port, said first input port and said second input port being placed at a first selected location and a second selected location on 20 the exterior of the head, respectively,

(b) detecting simultaneously, at a first detection port placed at a selected location on the exterior of the head, radiation that has migrated in the brain from said first input port to said first detection 25 port and, at a second detection port placed at second selected location on the exterior of the head, radiation that has migrated in the brain from said second input port to said second detection port,

(c) processing signals of said radiation detected 30 at said first and second detection port that have migrated in the brain to create first and second processed data, respectively, and

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(d) determining a selected property of said brain tissue by correlating said processed first and second data.

95. The method of claim 94 wherein said first 5 input port and said first output port are located on one parietal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the respective hemisphere of the brain, and said second input port and said second output 10 port are located on the other parietal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the other hemisphere of the brain.

96. The method of claim 94 wherein said first 15 input port and said first output port are located on one temporal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the respective hemisphere of the brain, and said second input port and said second output 20 port are located on the other temporal bone, separated by a predetermined distance, in order to localize migration of said radiation in a selected region of the other hemisphere of the brain.

97. The method of claim 94, 95 or 96 wherein said 25 processing comprises comparing electromagnetic radiation detected at said first and second detection ports to create processed data representing a differential signal.

98. The method of claim 97 wherein said selected 30 property of said brain tissue is a pathophysiological state of said tissue.

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99. A method of in vivo examination of a tissue of a human by measuring changes in electromagnetic radiation scattered and absorbed in a migration path in said tissue comprising

5 (a) introducing electromagnetic radiation of a selected wavelength into the tissue at a first input port placed at a selected location on said human,

10 (b) detecting, at a first detection port placed at a selected location on said human, radiation of said selected wavelength that has migrated in the first localized tissue of interest from said first input port to said first detection port,

15 (c) introducing electromagnetic radiation of said selected wavelength into the tissue at a second input port placed at a second selected location on said human,

20 (d) detecting, at a second detection port placed at a selected location on said human, radiation of said selected wavelength that has migrated in the second localized tissue of interest from said second input port to said second detection port, said first localized tissue of interest having normal physiological properties, said second localized tissue of interest being examined for pathophysiological changes,

25 (e) processing signals of said detected radiation that has migrated in said first and second localized tissues of interest to create first and second processed data, and

30 (f) determining pathophysiological changes in said second localized tissue of interest by correlating both said first and said second processed data.

100. The method of claim 99 wherein said radiation is simultaneously introduced at said first and second input ports and detected at said first and second detection ports.

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101. The method of claim 99 wherein said radiation  
is first introduced at said first input port and detected  
at said first detection port, and subsequently said  
radiation is introduced at said second input port and  
5 detected at said second detection port.

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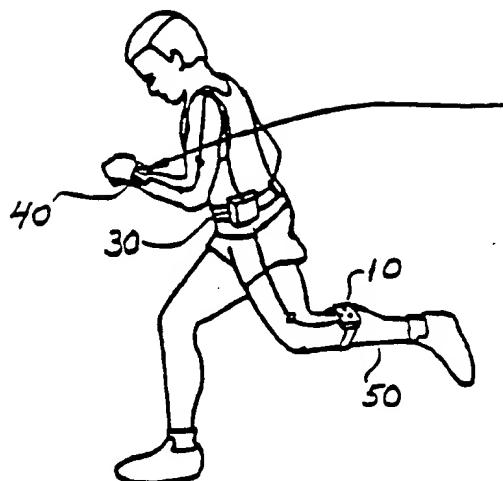


FIG. 1A

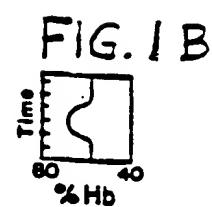


FIG. 1

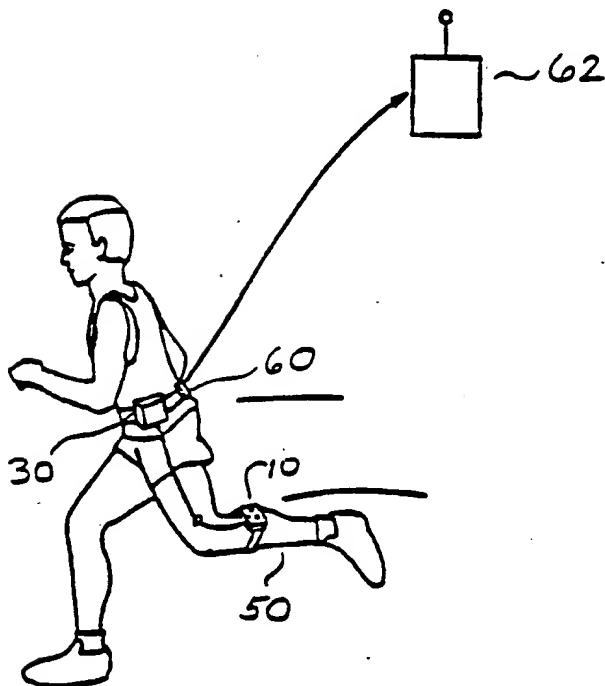


FIG. 3

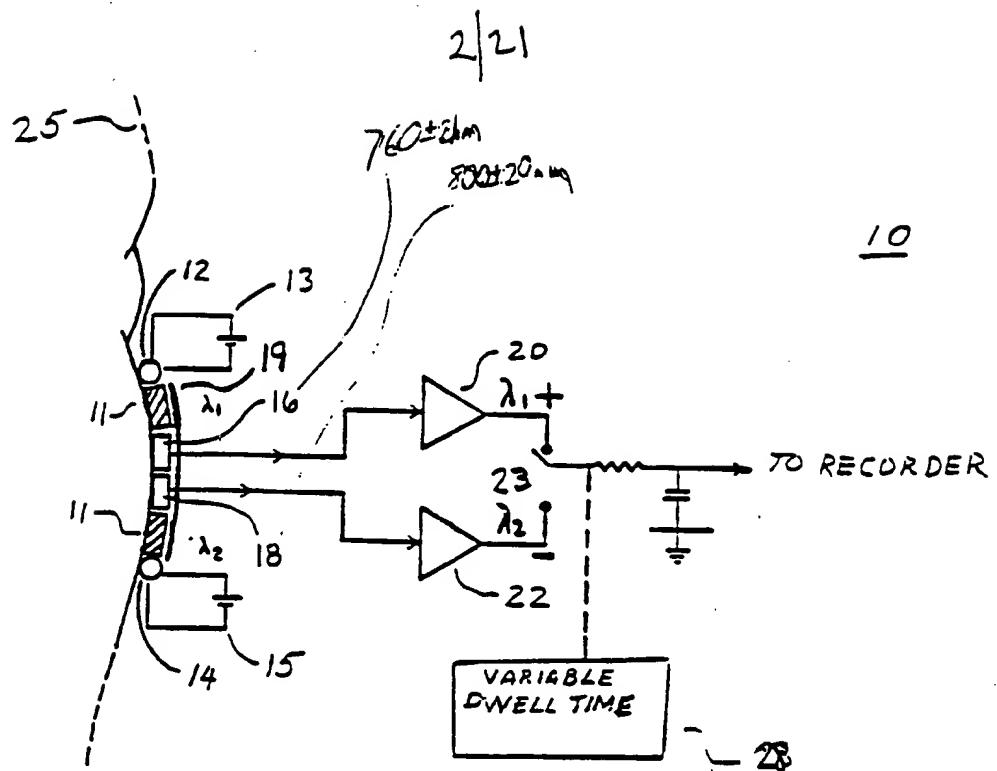


FIG. 2

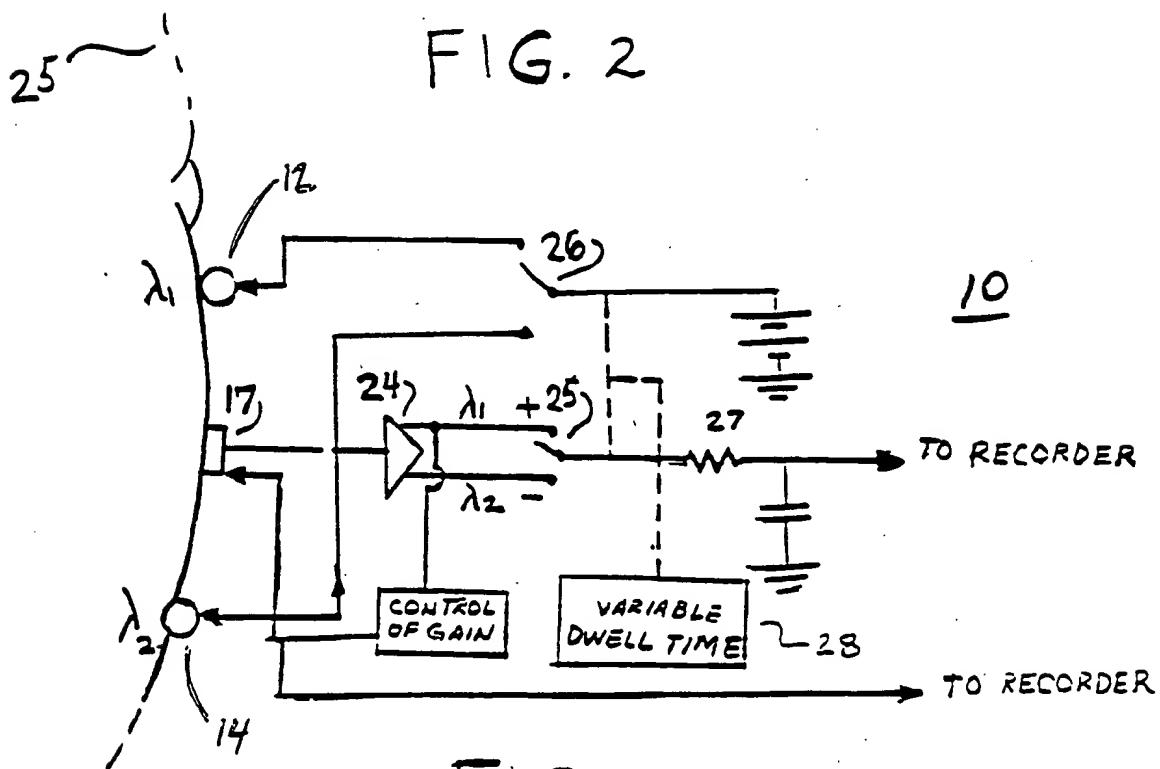
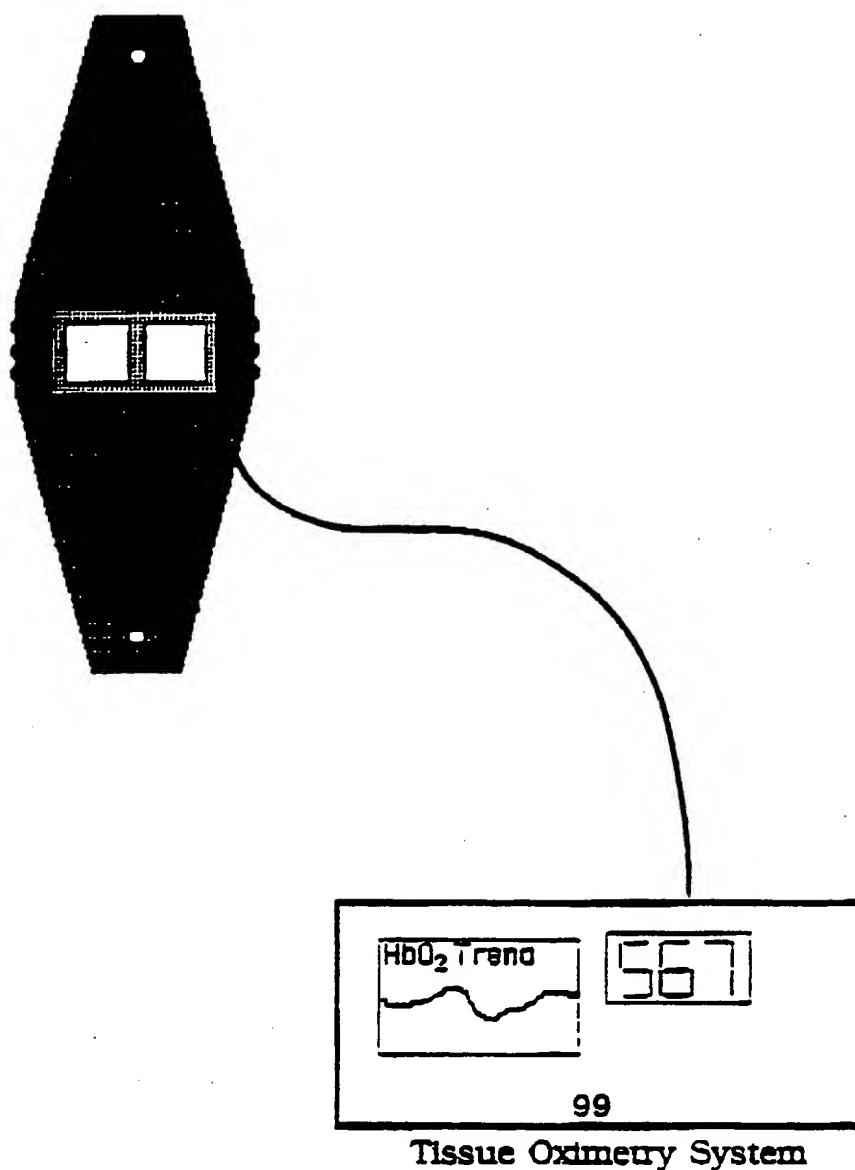


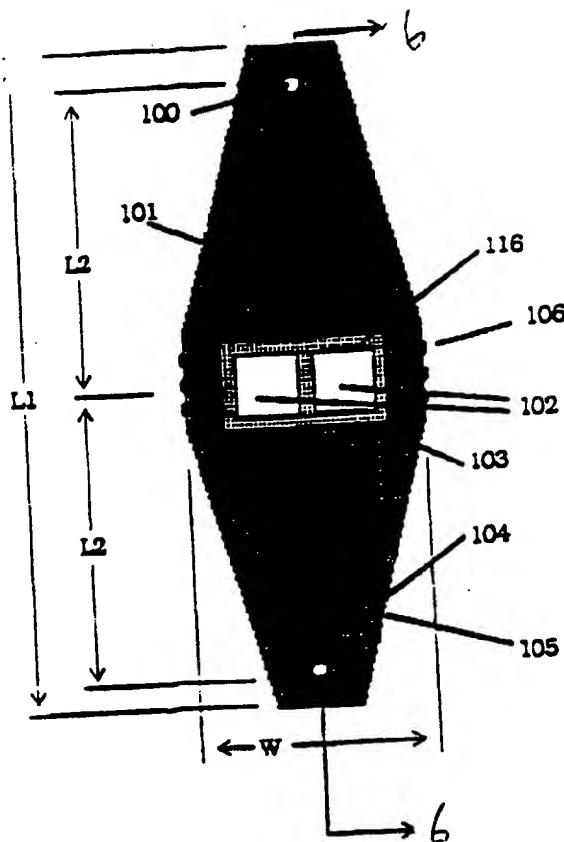
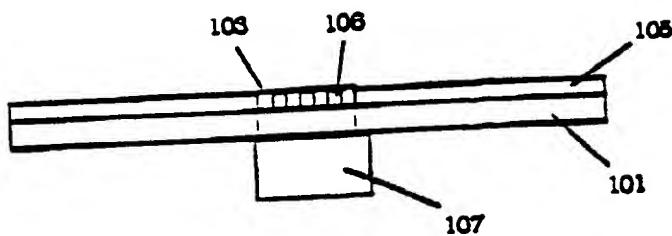
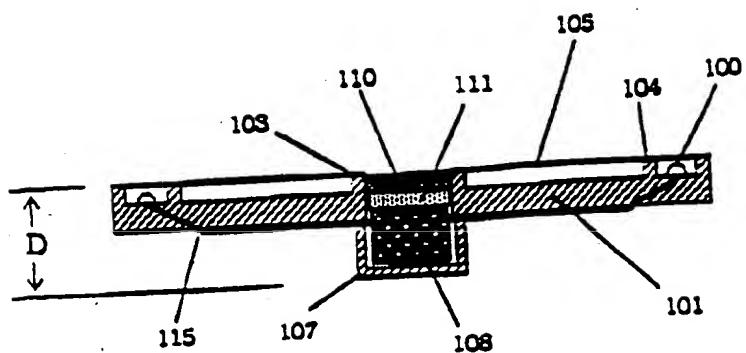
FIG. 4

321

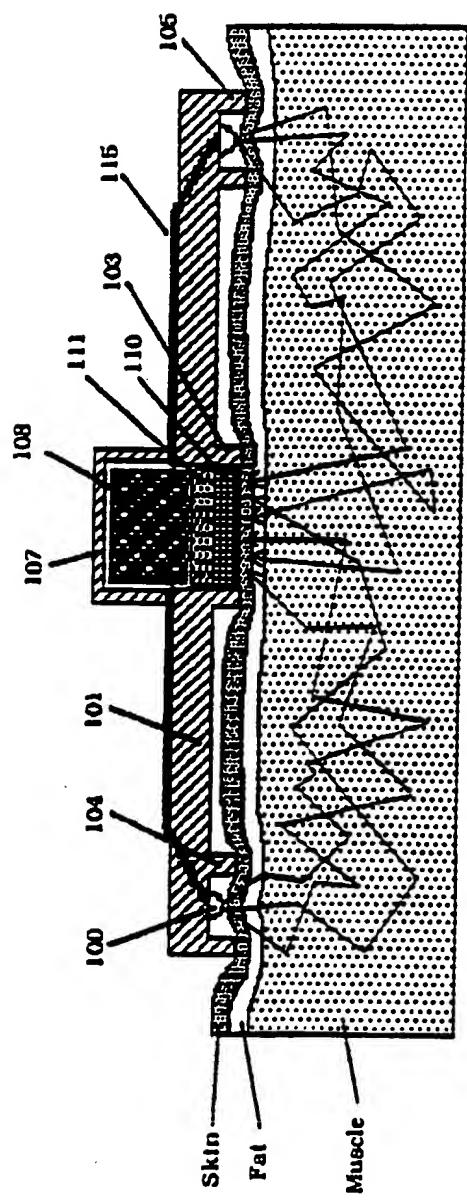


**Figure 5**

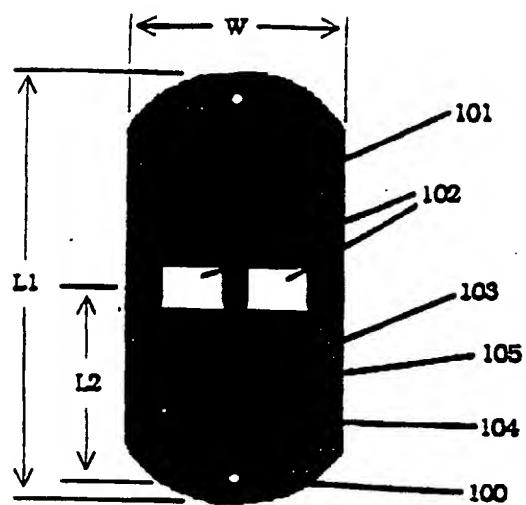
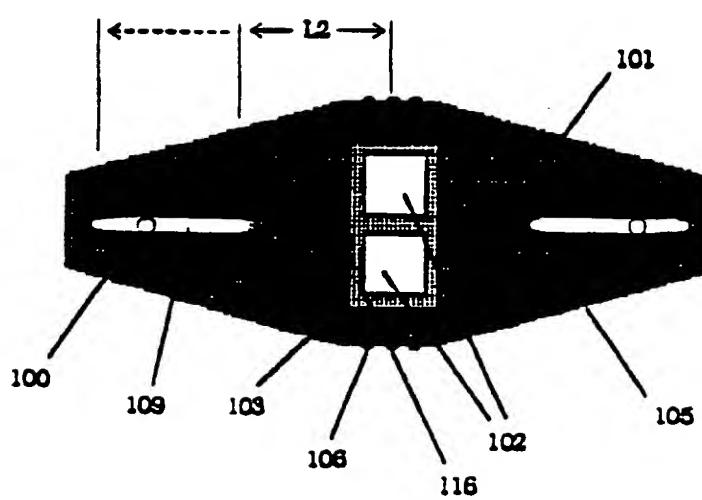
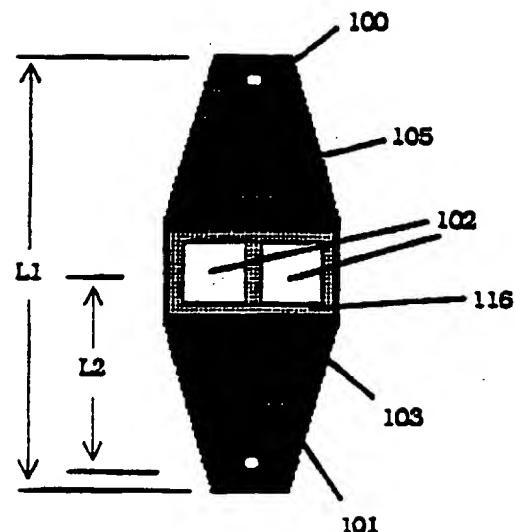
4/21

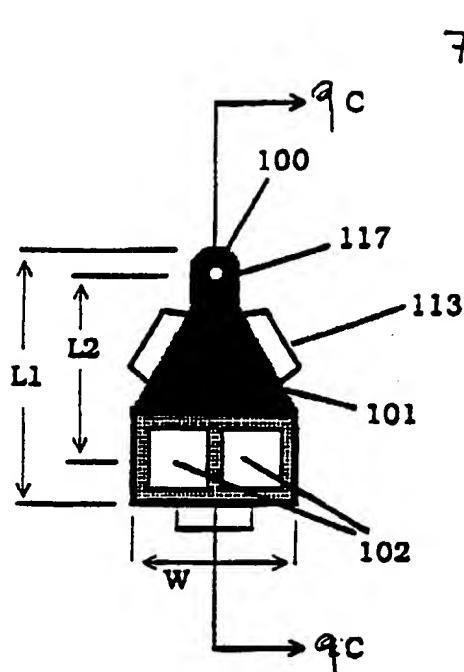
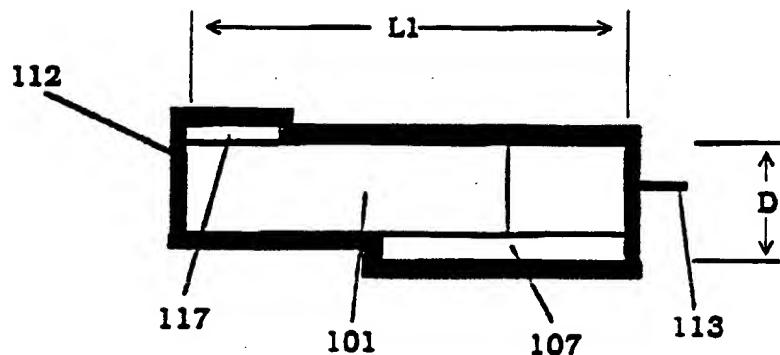
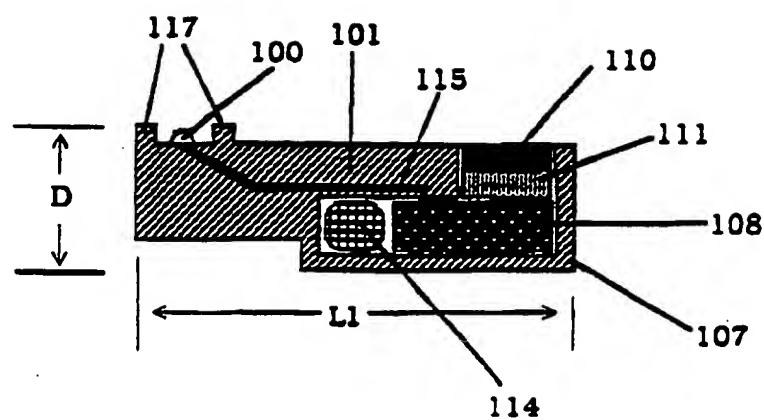
**Figure 6A****Figure 6B****Figure 6C**

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**Figure 7**

**Figure 8B**

**Figure 9A****Figure 9B****Figure 9C**

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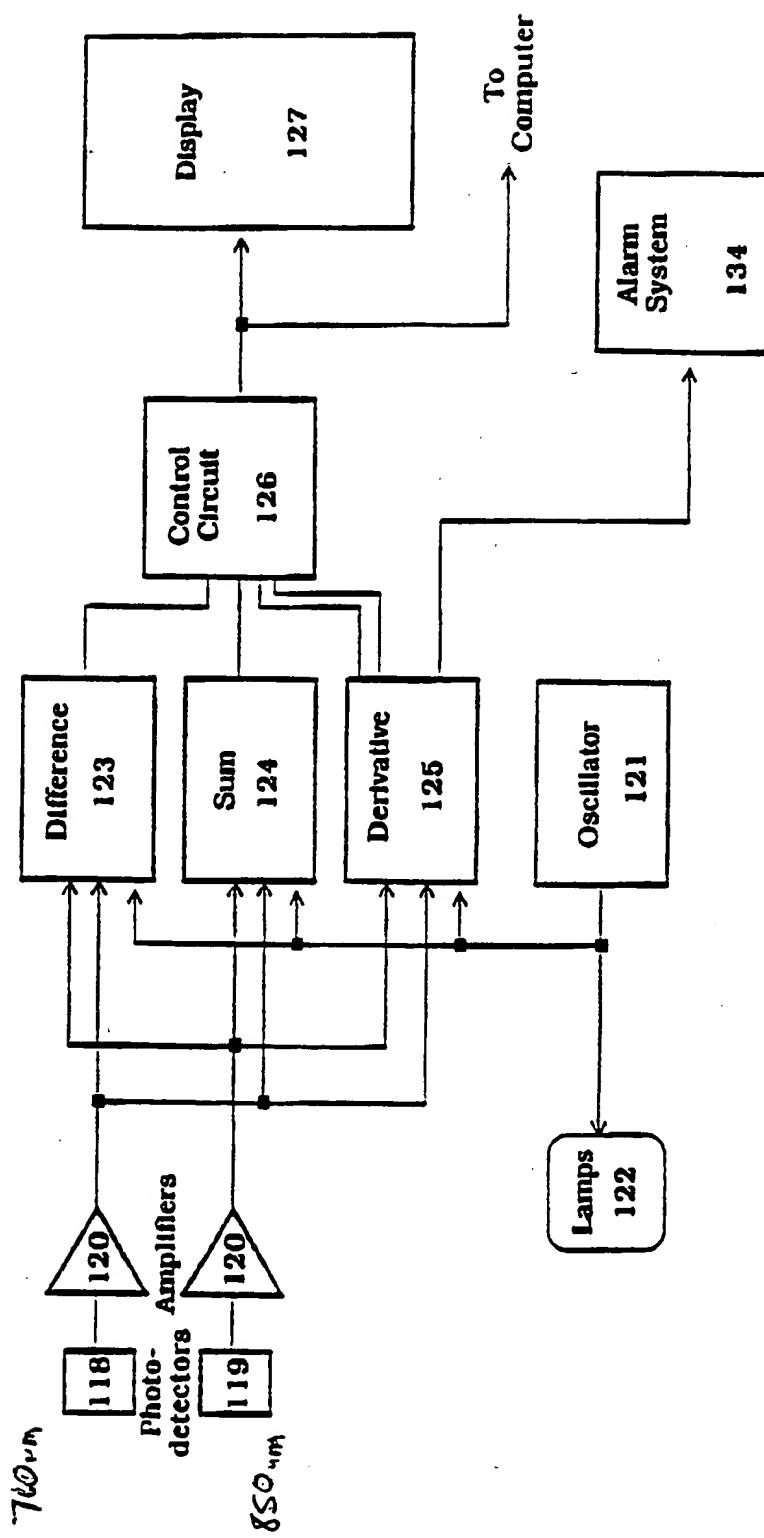
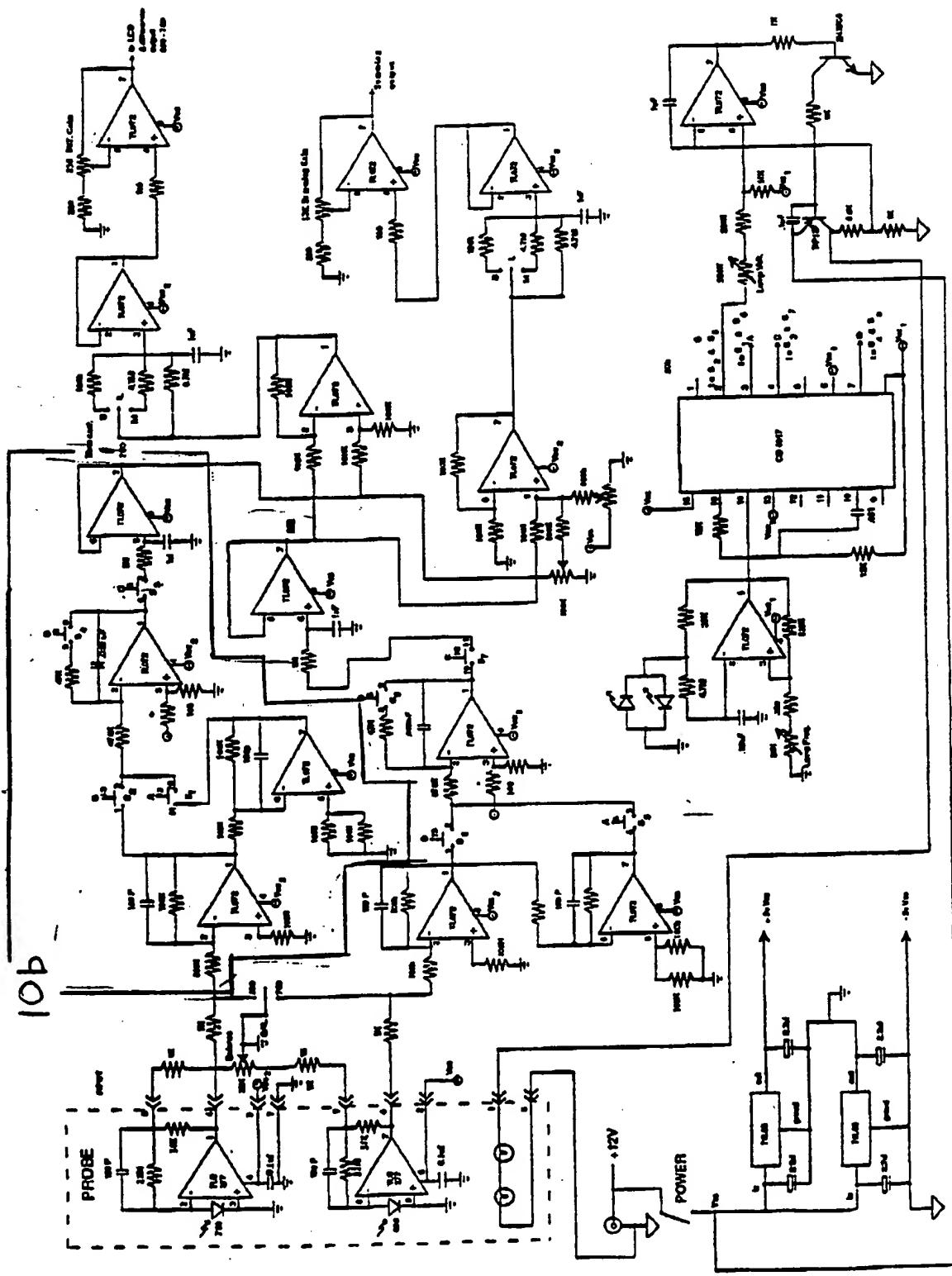


Figure 10

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FIG 10a

Run Monitor Circuit Diagram Nov 7, 1990

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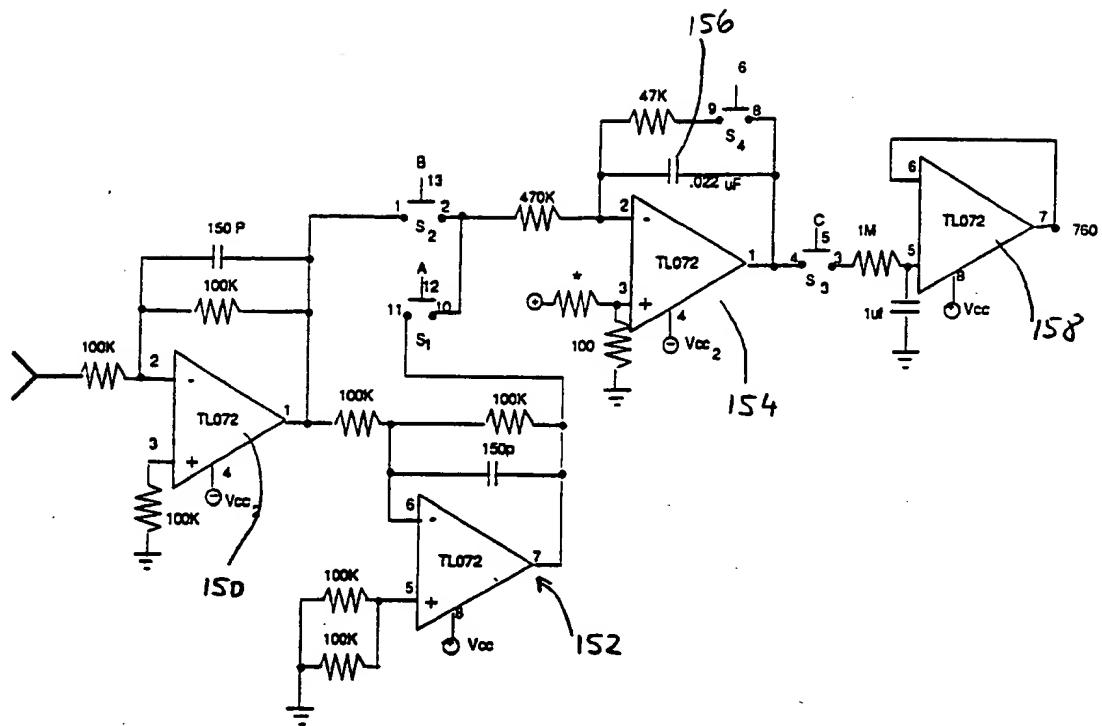


Fig. 106

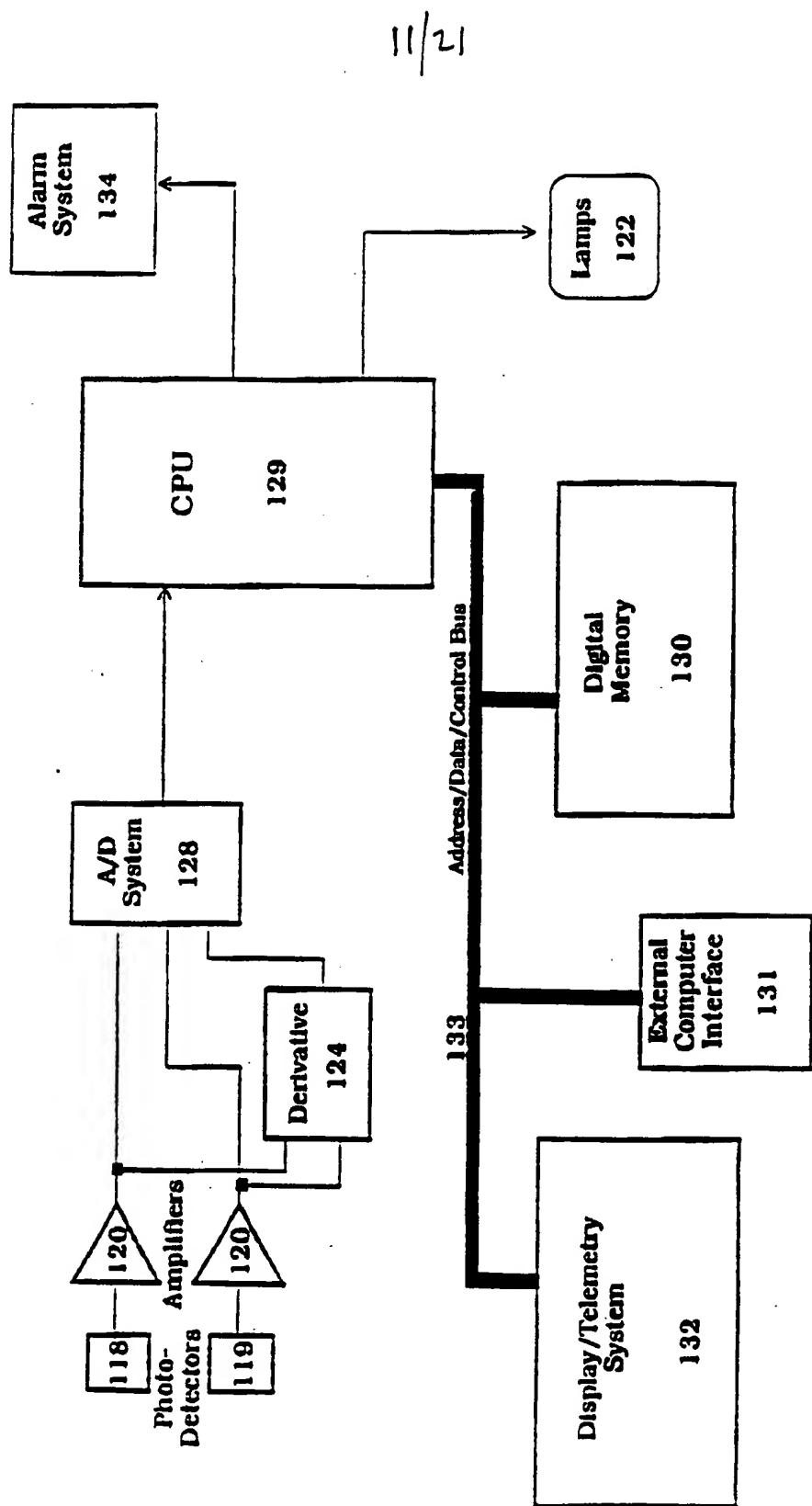
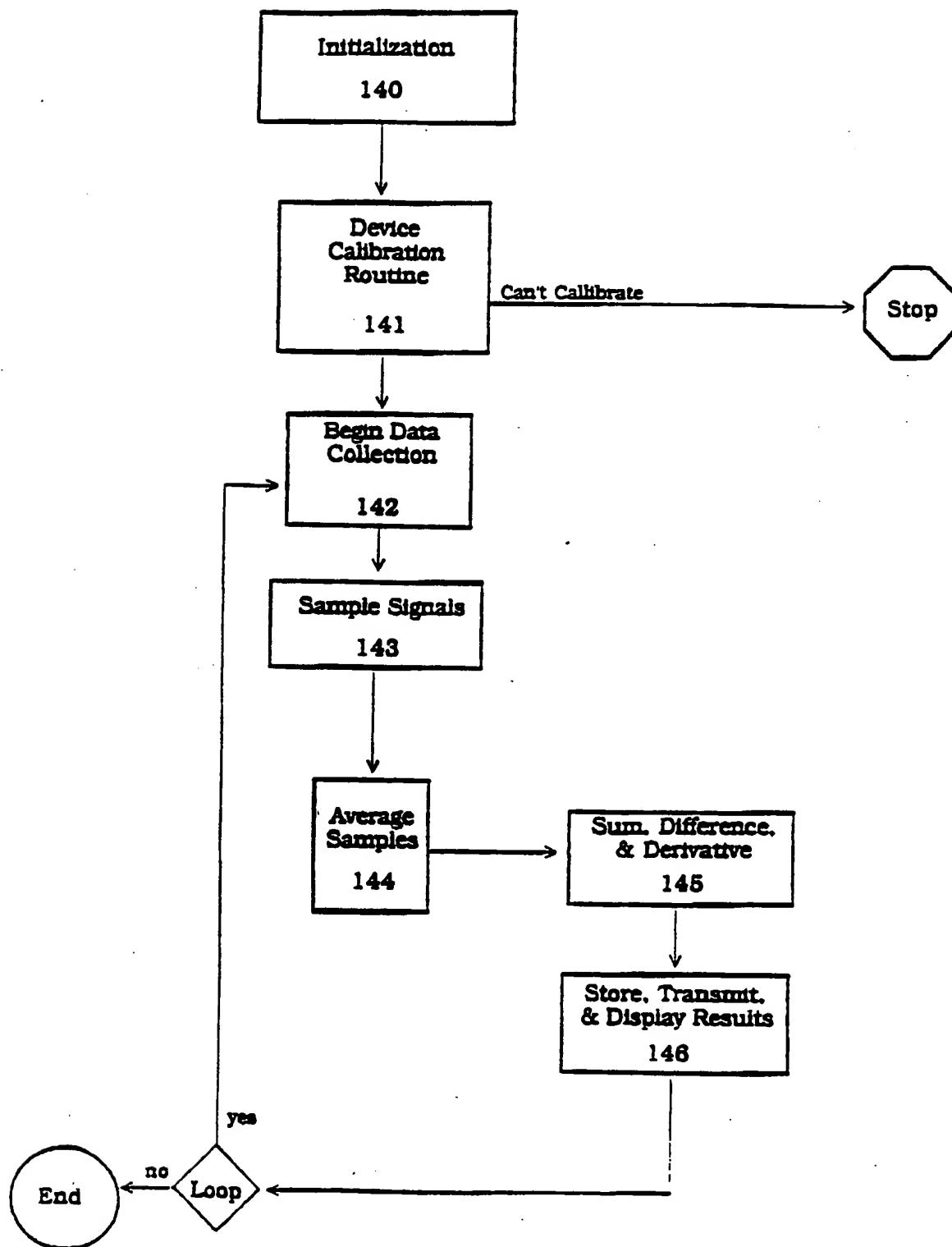


Figure 11

12|2|

**Figure 12**  
Software Flow Diagram



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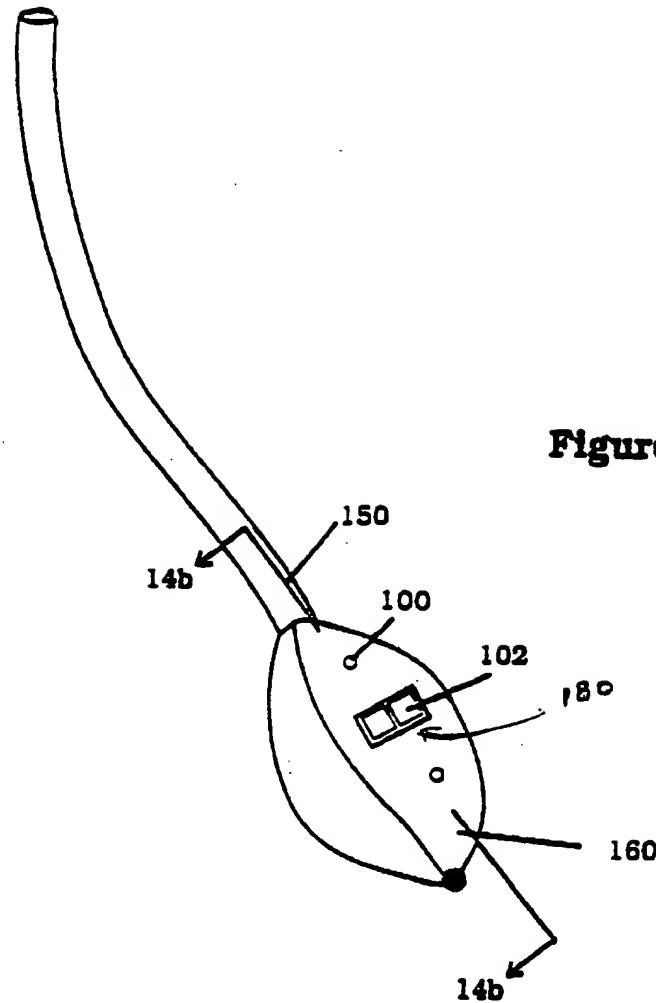


Figure 14a

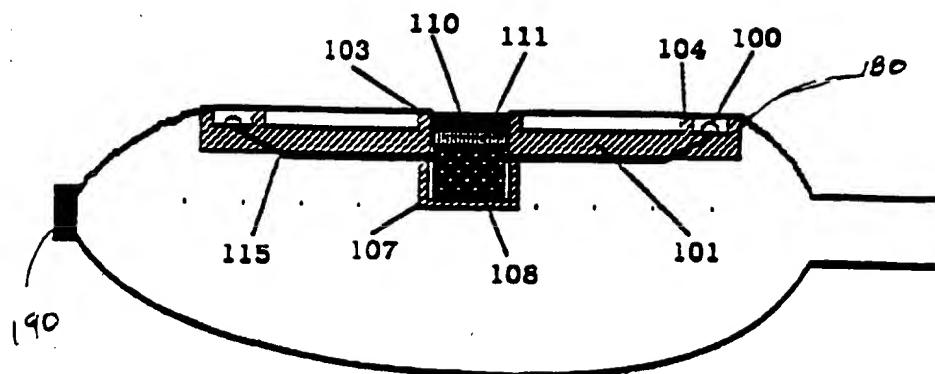


Figure 14b

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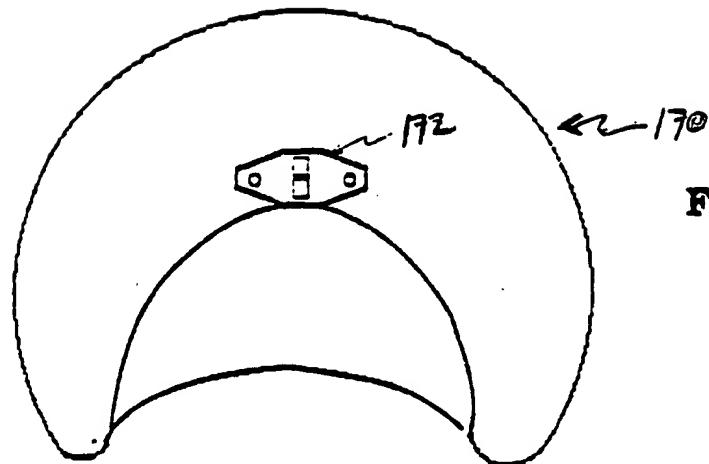


Figure 13

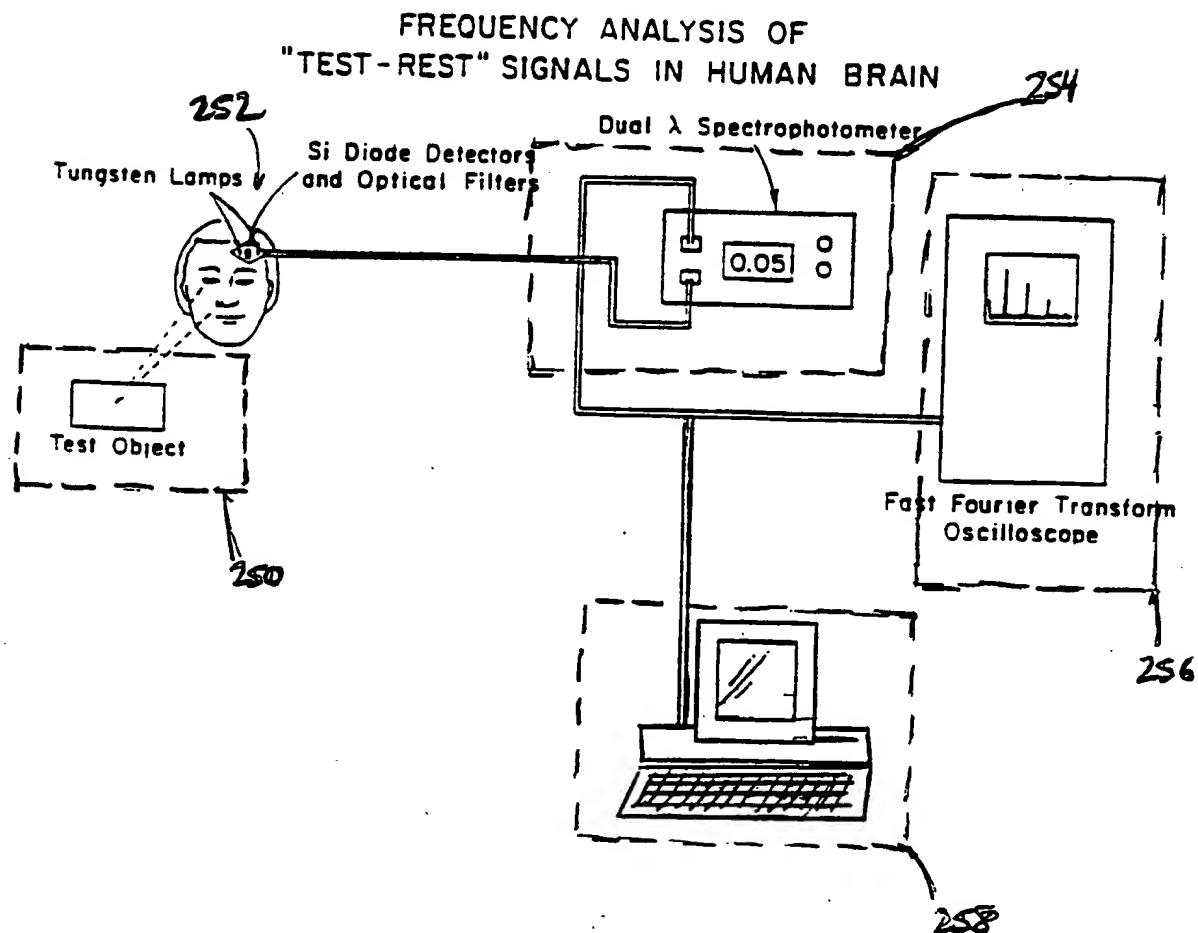


FIG 15

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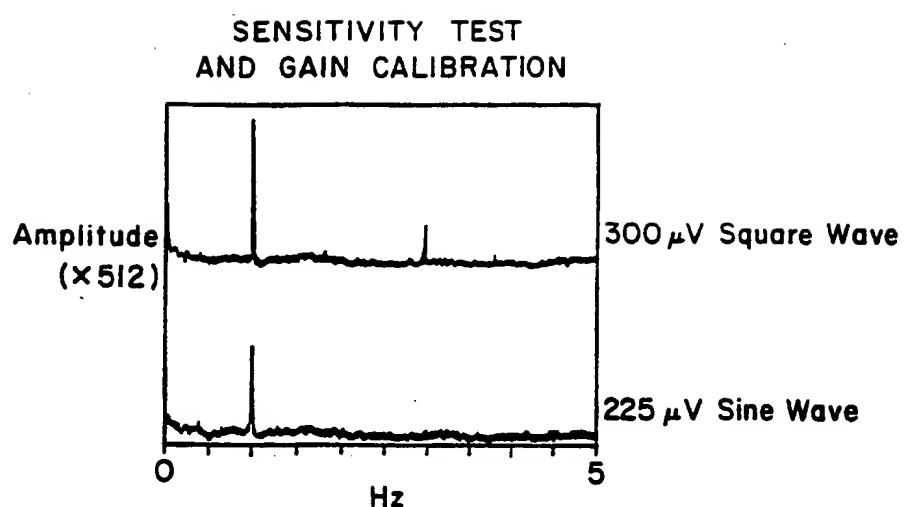


FIG 16 BC 120

## RESPONSE SPEED TEST

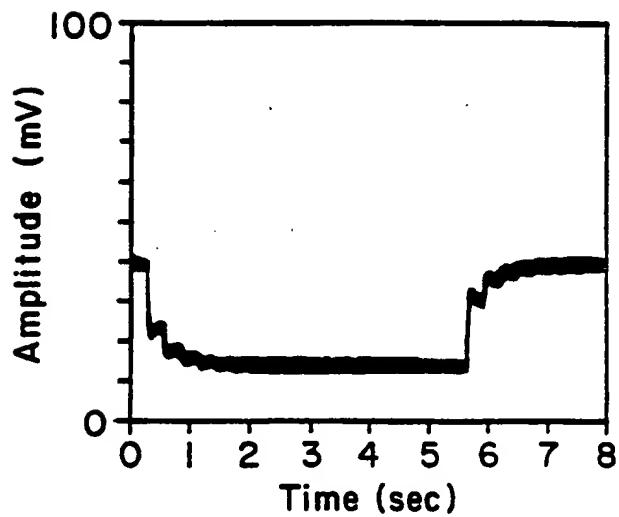


FIG. 17

BC 128

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SUBJECT U.  
07/31/91 81 BPM n = 16

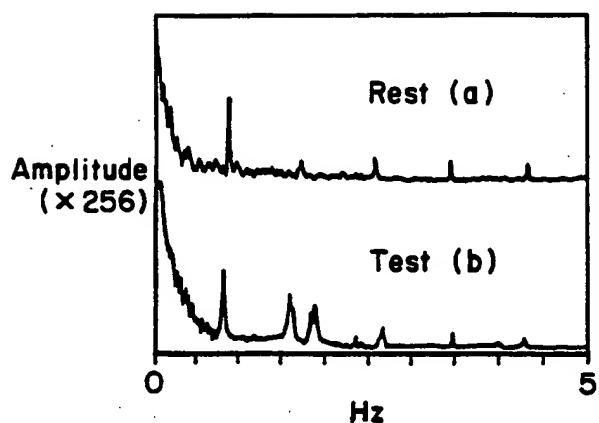


FIG 18a

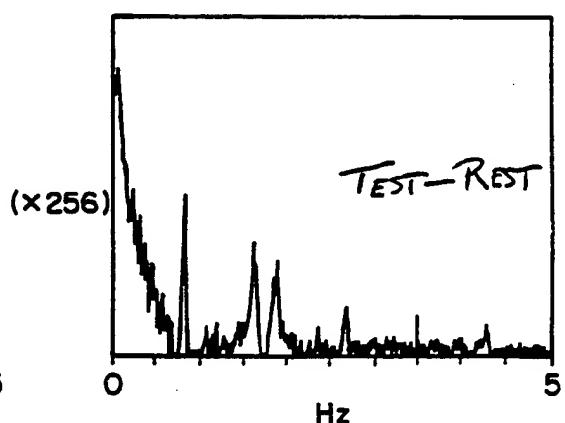


FIG 18b BC 115

SUBJECT B.  
07/30 n = 7

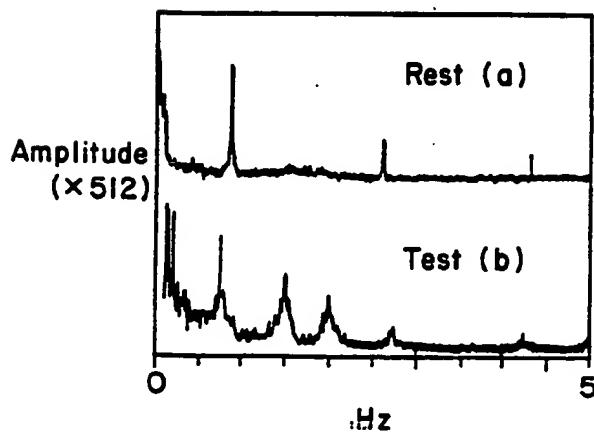


FIG 19a

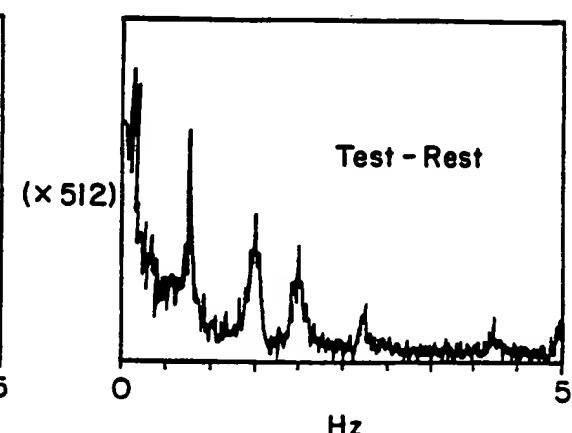


FIG 19b BC 116

17[2]

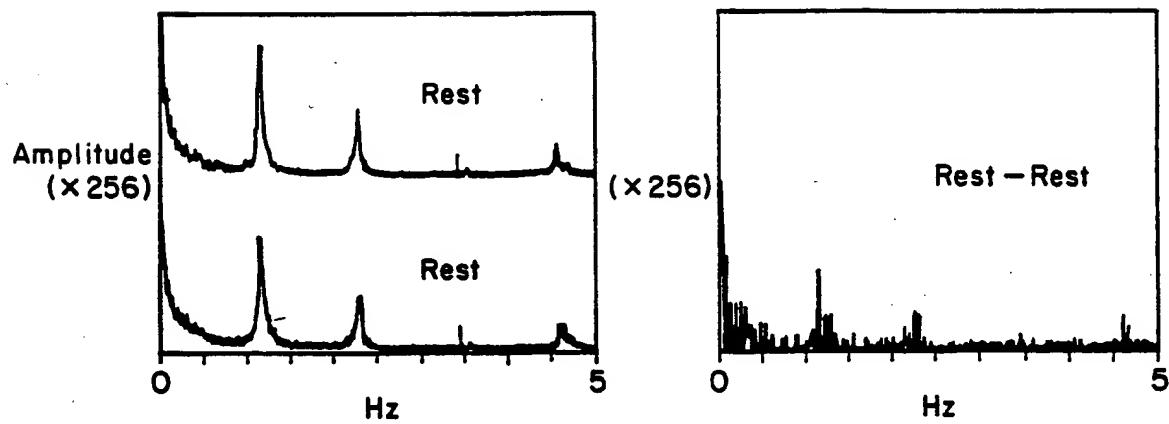
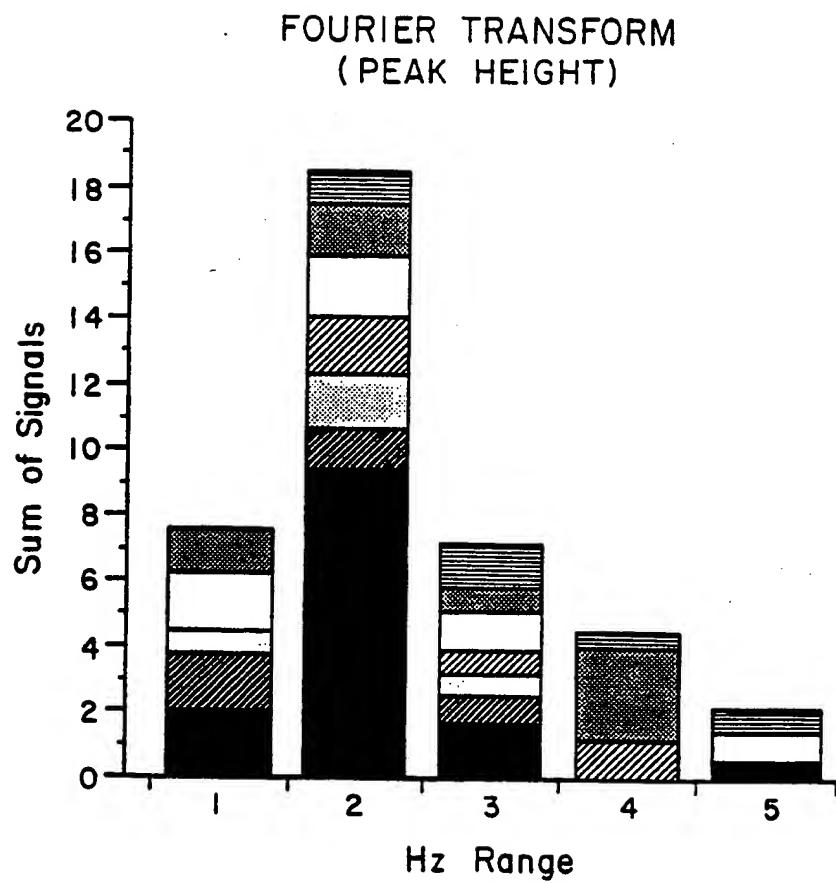
SUBJECT U.  
08/8/91 n=16

FIG 20a

FIG 20b

BC 121

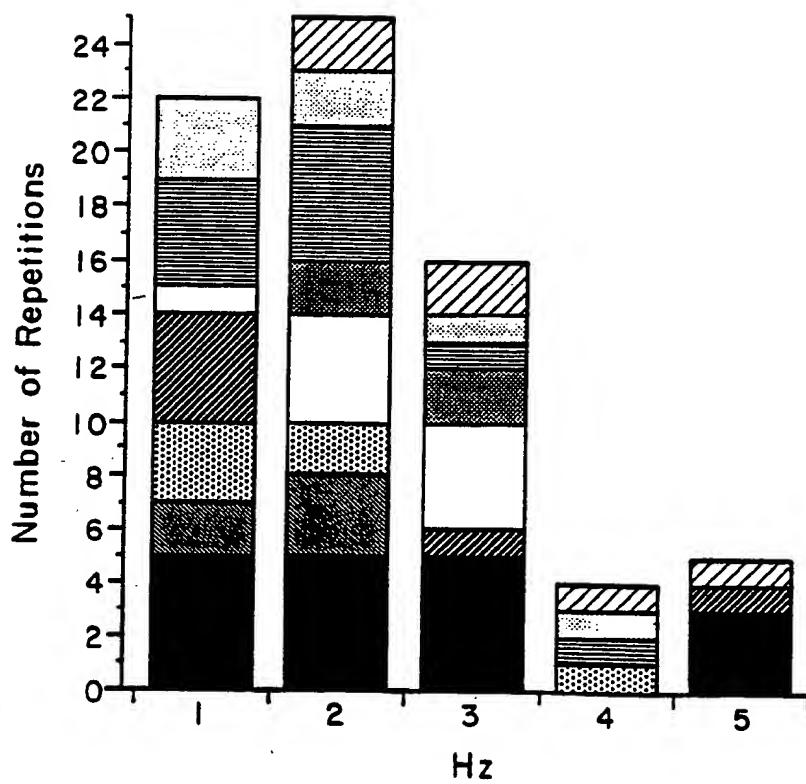
1821



BC 132

Fig 21

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FOURIER TRANSFORM  
(DIFFERENCE)

BC 131

Fig 2/9

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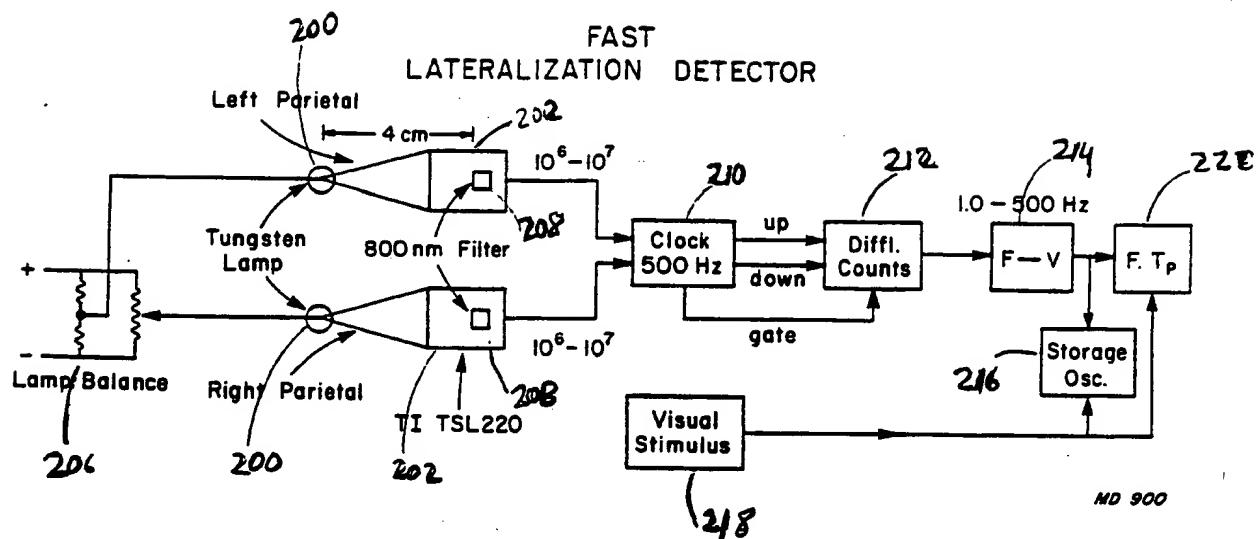


Fig. 22

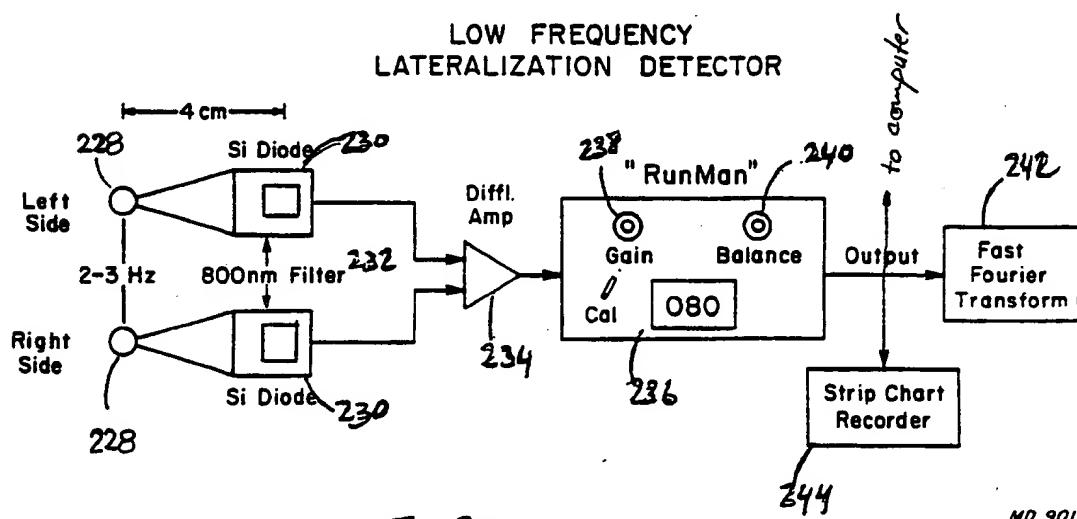


Fig. 23

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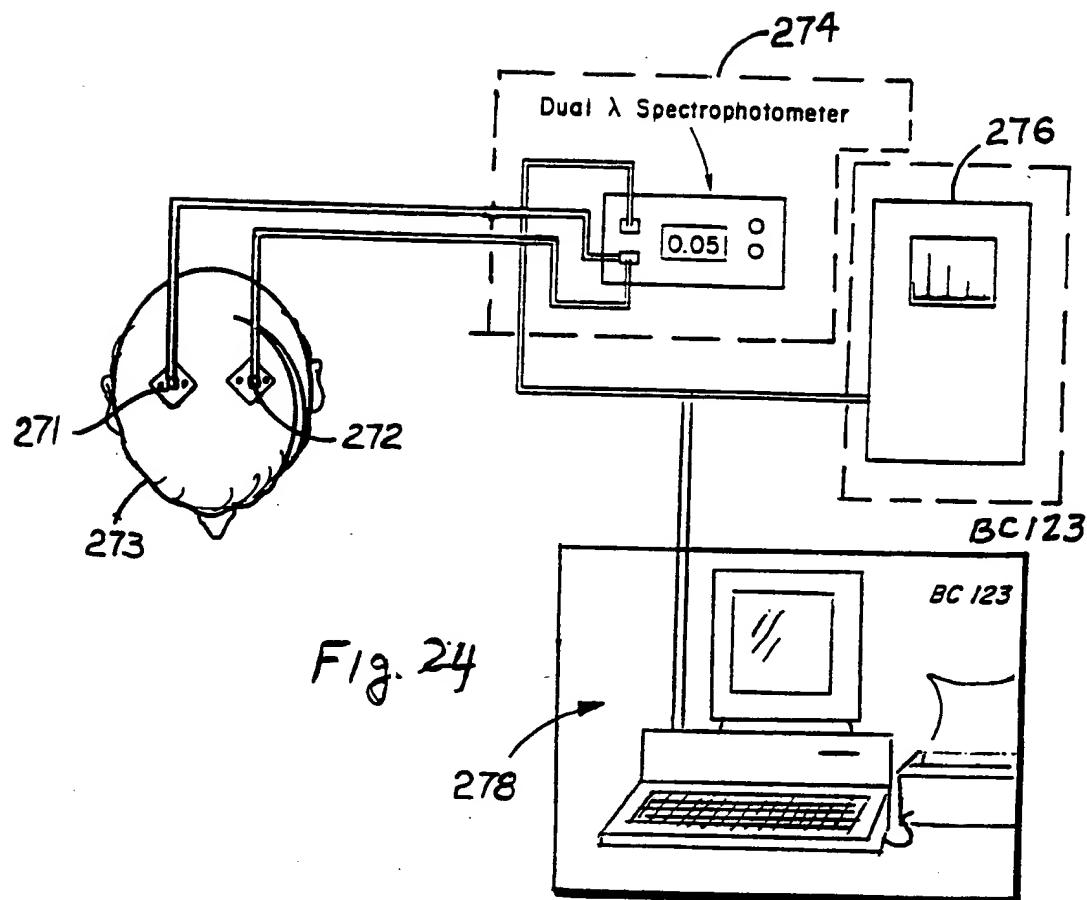


Fig. 24